Tetrahedron
Volume 53, Issue 32 , 11 August 1997, Pages 10953-10970

doi:10.1016/S0040-4020(97)00357-8 Cite or Link Using DOI

Convergent catalytic asymmetric synthesis of camptothecin analog GI147211C

This paper is dedicated to Professor Samuel J. Danishefsky in recognition of his many contributions to the field of organic chemistry.

Francis G. Fang*, Donald D. Bankston[2], Edward M. Huie, M. Ross Johnson[3], Myung-Chol Kang[3], Craig S. LeHoullier, George C. Lewis[4], Thomas C. Lovelace, Melissa W. Lowery, Darryl L. McDougald, Clive A. Meerholz, John J. Partridge, Matthew J. Sharp and Shiping Xie

Chemical Development Department, Glaxo Wellcome Inc., Research Triangle Park, North Carolina 27709, USA

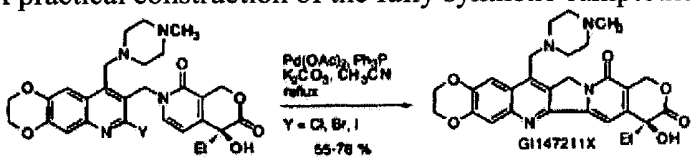
Received 27 September 1996; accepted 10 January 1997. ; Available online 2 April 1998.

Abstract

The topoisomerase **I** inhibitor GI147211C (**4**) was discovered at Glaxo Wellcome and shown to have promising anti-cancer properties. In order to fully assess the clinical potential of **4**, an improved synthesis of the drug substance was required. Herein is described a convergent catalytic asymmetric synthesis of **4** which utilizes as key steps, two Heck reactions, a Sharpless asymmetric dihydroxylation reaction, and a Mitsunobu reaction. A 2-chloroquinoline is shown to be a viable substrate for the final Heck reaction to generate the camptothecin nucleus.

Graphical Abstract

A practical construction of the fully synthetic camptothecin analog GI147211C is described.



[2] Current address: Miles Inc., West Haven, CT 06516-4175

[3] Current address: Trimeris Inc., Durham, NC 27707

[4] Current address: Amgen Inc., Boulder, CO

Tetrahedron
Volume 53, Issue 32 , 11 August 1997, Pages 10953-10970

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FULL ESTIMATED COST	0.21	0.21

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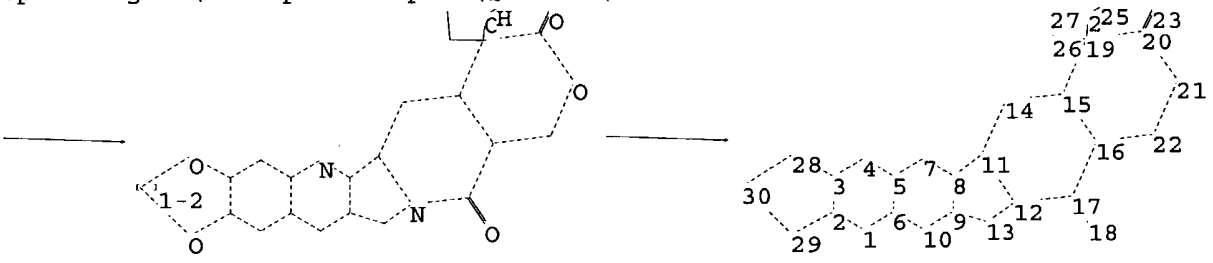


chain nodes :
18 23 24 25 26 27
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 19 20 21 22 28 29
30
chain bonds :
17-18 19-24 19-26 20-23 24-25 26-27
ring bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 19-20 20-21 21-22
28-30 29-30
exact/norm bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 17-18 19-20 19-24
20-21 20-23 21-22 28-30 29-30
exact bonds :
19-26 24-25 26-27

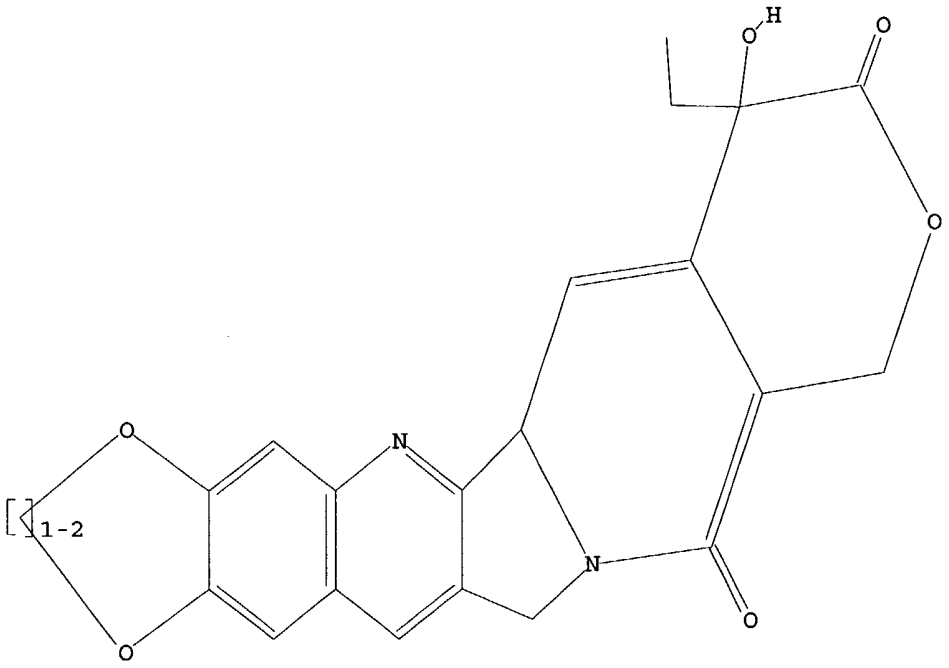
Match level :

6/24/04

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:Atom 29:Atom 30:Atom
fragments assigned product role:
containing 1

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED - 40 TO ITERATE

100.0% PROCESSED 40 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 421 TO 1179
PROJECTED ANSWERS: 0 TO 0

L2 0 SEA SSS SAM L1

=> s l1 ful

6/24/04

FULL SEARCH INITIATED 16:31:21 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 708 TO ITERATE

100.0% PROCESSED 708 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

L3 0 SEA SSS FUL L1

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	161.72	161.93

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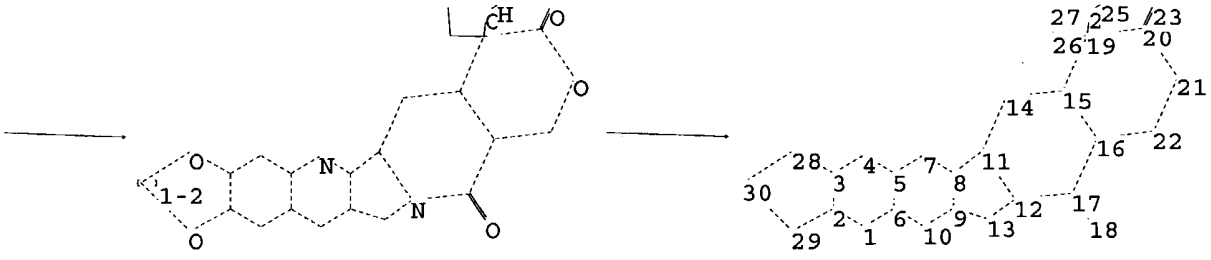

chain nodes :
18 23 24 25 26 27
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 19 20 21 22 28 29
30

10/606795

6/24/04

chain bonds :
17-18 19-24 19-26 20-23 24-25 26-27
ring bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 19-20 20-21 21-22
28-30 29-30
exact/norm bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 17-18 19-20 19-24
20-21 20-23 21-22 28-30 29-30
exact bonds :
19-26 24-25 26-27

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:Atom 29:Atom 30:Atom
fragments assigned product role:
containing 1

L4 STRUCTURE UPLOADED

=> d l4
L4 HAS NO ANSWERS
L4 STR

Structure diagram not available for display

Structure attributes must be viewed using STN Express query preparation.

=> s l4
SAMPLE SEARCH INITIATED 16:40:28 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 30 TO ITERATE

100.0% PROCESSED 30 ITERATIONS 21 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 272 TO 928
PROJECTED ANSWERS: 146 TO 694

L5 21 SEA SSS SAM L4

=> s l4 ful
FULL SEARCH INITIATED 16:40:37 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 534 TO ITERATE

100.0% PROCESSED 534 ITERATIONS 356 ANSWERS
SEARCH TIME: 00.00.01

L6 356 SEA SSS FUL L4

```
=> file caplus
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       155.42     317.35

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FILE COVERS 1907 - 24 Jun 2004  VOL 140 ISS 26
FILE LAST UPDATED: 23 Jun 2004  (20040623/ED)

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=> s l6
L7          166 L6

=> file registry
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.88     318.23

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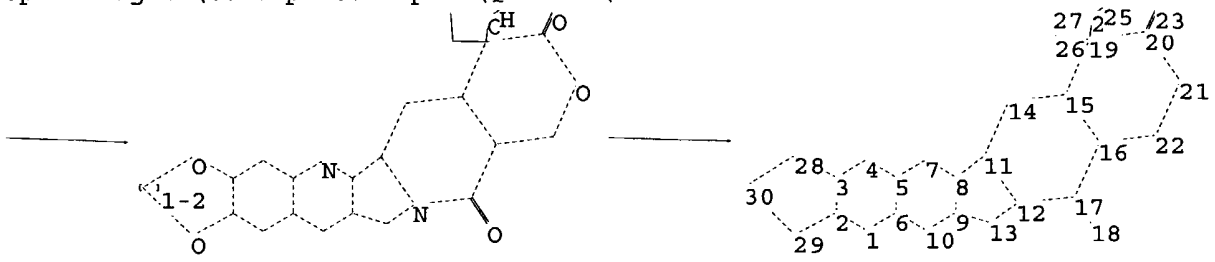

chain nodes :
18 23 24 25 26 27
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 19 20 21 22 28 29
30
chain bonds :
17-18 19-24 19-26 20-23 24-25 26-27
ring bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 19-20 20-21 21-22
28-30 29-30
exact/norm bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 17-18 19-20 19-24
20-21 20-23 21-22 28-30 29-30
exact bonds :
19-26 24-25 26-27

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:Atom 29:Atom 30:Atom
fragments assigned product role:
containing 1

L8 STRUCTURE UPLOADED

=> d l8
L8 HAS NO ANSWERS
L8 STR

Structure diagram not available for display

Structure attributes must be viewed using STN Express query preparation.

6/24/04

```
=> s l8
SAMPLE SEARCH INITIATED 16:41:59 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     30 TO ITERATE

100.0% PROCESSED      30 ITERATIONS                              21 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          272 TO      928
PROJECTED ANSWERS:             146 TO      694

L9           21 SEA SSS SAM L8

=> s l8 ful
FULL SEARCH INITIATED 16:42:05 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    534 TO ITERATE

100.0% PROCESSED     534 ITERATIONS                             356 ANSWERS
SEARCH TIME: 00.00.01

L10          356 SEA SSS FUL L8

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   155.42     473.65

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=> s l10
L11          166 L10

=> file registry
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.88     474.53
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10/606795

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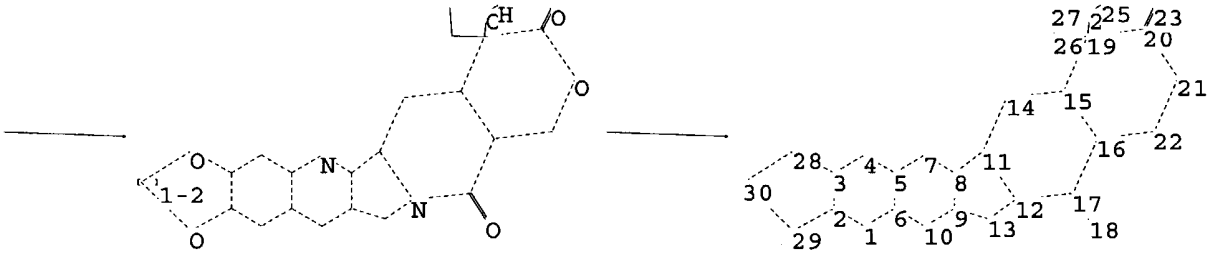

chain nodes :
18 23 24 25 26 27
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 19 20 21 22 28 29
30
chain bonds :
17-18 19-24 19-26 20-23 24-25 26-27
ring bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 19-20 20-21 21-22
28-30 29-30
exact/norm bonds :
1-2 1-6 2-3 2-29 3-4 3-28 4-5 5-6 5-7 6-10 7-8 8-9 8-11 9-10 9-13
11-12 11-14 12-13 12-17 14-15 15-16 15-19 16-17 16-22 17-18 19-20 19-24
20-21 20-23 21-22 28-30 29-30
exact bonds :

19-26 24-25 26-27

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom 18:CLASS 19:Atom
20:Atom 21:Atom 22:Atom 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:Atom 29:Atom 30:Atom
fragments assigned product role:
containing 1

L12   STRUCTURE UPLOADED

=> d l12
L12 HAS NO ANSWERS
L12   STR

Structure diagram not available for display

Structure attributes must be viewed using STN Express query preparation.

=> s l12
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SAMPLE SCREEN SEARCH COMPLETED -   30 TO ITERATE

100.0% PROCESSED   30 ITERATIONS   21 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS: 272 TO   928
PROJECTED ANSWERS: 146 TO   694

L13   21 SEA SSS SAM L12

=> s l12 ful
FULL SEARCH INITIATED 16:44:16 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   534 TO ITERATE

100.0% PROCESSED   534 ITERATIONS   356 ANSWERS
SEARCH TIME: 00.00.01

L14   356 SEA SSS FUL L12

=> file caplus
COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                   ENTRY   SESSION
FULL ESTIMATED COST   155.42   629.95

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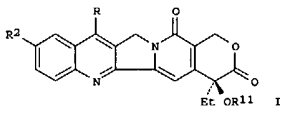
FILE COVERS 1907 - 24 Jun 2004 VOL 140 ISS 26
FILE LAST UPDATED: 23 Jun 2004 (20040623/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l14
L15 166 L14

=> d abs bib fhitstr 20-30

L15 ANSWER 20 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI



AB Camptothecin amino acid ester prodrug analogs, such as I [R = -X-SiR6R7R8;
X = bond or connecting alkylene, alkenylene, or alkynylene group ;R2 = H, OH, CN, NO2, N3, CHO, SH, halogen, alkyl, alkenyl, alkynyl, alkoxy, aryloxy, acyloxy, etc.; R6, R7, R8 = alkyl, alkenyl, alkynyl, aryl, etc.; R11 = CO(CH2)nNR16R17; R16, R17 = H, alkyl, alkenyl, alkynyl, etc.; NR16R17 = nitrogen bound heterocyclyl; n = 1-30], of highly lipophilic silatecans of potential use in the treatment of cancer and AIDS. Thus,
DB
172 I [R = (CH2)2SiMe3, R2 = R11 = H] was O-acylated with BOC-NHCH2CO2H using DMAP in CH2Cl2 to form the N-protected glycine ester I [R = (CH2)2SiMe3, R2 = H, R11 = COCH2NHCO2CMe3] with 48% yield. The protected glycine ester was then converted to the hydrochloride salt of I [R = (CH2)2SiMe3, R2 = H, R11 = COCH2NH2] with 91% yield. using HCl in dioxane.
Lipophilicity, fluorescence anisotropy, and equilibrium binding consts. of the
prepared camptothecin amino acid ester prodrugs were assayed.
AN 2002:615405 CAPLUS
DN 137:169684
TI Preparation and formulation of highly lipophilic camptothecin prodrugs for
therapeutic use in the treatment of cancer and AIDS
IN Bom, David C.; Burke, Thomas G.
PA University of Kentucky Research Foundation, USA
SO PCT Int. Appl., 343 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002062340	A1	20020815	WO 2002-US3548	20020206

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,

L15 ANSWER 20 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
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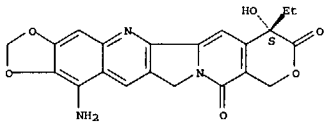
OS MARPAT 137:169684
IT **135014-21-0P**
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and formulation of highly lipophilic camptothecin prodrugs for
therapeutic use in the treatment of cancer and AIDS)
RN 135014-21-0 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 21 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB The invention provides combinations of a DNA topoisomerase I inhibiting agent and a selective COX-2 inhibiting agent for preventing, treating, and/or reducing the risk of developing a neoplasia disorder in a mammal. Compound preparation is included.
AN 2002:575747 CAPLUS
DN 137:135070
TI DNA topoisomerase I inhibitor-cyclooxygenase 2 inhibitor antiangiogenic combination for the treatment of cancer
IN McKearn, John P.; Gordon, Gary B.; Cunningham, James; Gately, Stephen T.; Koki, Alane T.; Masferrer, Jaime L.
PA USA
SO U.S. Pat. Appl. Publ., 97 pp., Cont.-in-part of U.S. Ser. No. 470,951.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 19

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002103141	A1	20020801	US 2001-843132	20010425
WO 2002085459	A2	20021031	WO 2002-US13219	20020425
WO 2002085459	A3	20040304		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1414526	A2	20040506	EP 2002-731524	20020425

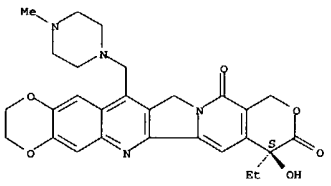
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

NO 2003004780	A	20031212	NO 2003-4780	20031024
PRAI US 1998-113786P	P	19981223		
US 1999-470951	A2	19991222		
US 2001-843132	A	20010425		
WO 2002-US13219	W	20020425		

OS MARPAT 137:135070
IT **149882-10-0**, Lurtotecan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(DNA topoisomerase I inhibitor-cyclooxygenase 2 inhibitor antiangiogenic combination for treatment of cancer)
RN 149882-10-0 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L15 ANSWER 21 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L15 ANSWER 22 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB Depletion of glutathione (GSH) in MCF-7 and MDA-MB-231 cell lines by pretreatment with the GSH synthesis inhibitor buthionine sulfoximine potentiated the activity of 10,11-methylenedioxy-20(S)-camptothecin, SN-38 [7-ethyl-10-hydroxy-20(S)-camptothecin], topotecan, and 7-chloromethyl-10,11-methylenedioxy-20(S)-camptothecin (CMMDC). The greatest potentiation was observed with the alkylating camptothecin CMMDC. Buthionine sulfoximine pretreatment also increased the number of camptothecin-induced DNA-protein crosslinks, indicating that GSH affects the mechanism of action of camptothecin. We also report that GSH interacts with CMMDC to form a stable conjugate, 7-(glutathionylmethyl)-10,11-methylenedioxy-20(S)-camptothecin (GSMMDC), which is formed spontaneously in buffered solns. and in MCF-7 cells treated with CMMDC. GSMMDC was synthesized and found to be nearly as active as 10,11-methylenedioxy-20(S)-camptothecin in a topoisomerase (topo) I-mediated DNA nicking assay. The resulting topo I cleavage complexes were remarkably stable. In cell culture, GSMMDC displayed potent growth-inhibitory activity against U937 and P388 leukemia cell lines. GSMMDC was not active against a topo I-deficient P388 cell line, indicating that topo I is its cellular target. Peptide-truncated analogs of GSMMDC were prepared and evaluated. All three derivs. [7-(γ-glutamylcysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, 7-(cysteinylglycylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, and 7-(cysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin] displayed topo I and cell growth-inhibitory activity. These results suggest that 7-peptidyl derivs. represent a new class of camptothecin analogs.

AN 2002:550586 CAPLUS

DN 138:162968

TI Dual role of glutathione in modulating camptothecin activity: depletion potentiates activity, but conjugation enhances the stability of the topoisomerase I-DNA cleavage complex

AU Gamcsik, Michael P.; Kasibhatla, Mohit S.; Adams, David J.; Flowers, James L.; Colvin, O. Michael; Manikumar, Govindarajan; Wani, Mansukh; Wall, Monroe E.; Kohlhagen, Glenda; Pommier, Yves

CS Department of Medicine, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC, 27710, USA

SO Molecular Cancer Therapeutics (2001), 1(1), 11-20
CODEN: MCTOCP; ISSN: 1535-7163

PB American Association for Cancer Research

DT Journal

LA English

OS CASREACT 138:162968

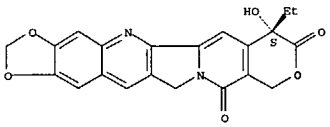
IT **135415-73-5**, 10,11-Methylenedioxy-20(S)-camptothecin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

RN 135415-73-5 CAPLUS

L15 ANSWER 22 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 23 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB The invention discloses the use of incensole and/or furanogermacrens, deriva. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

AN 2002:521462 CAPLUS

DN 137:88442

TI Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms

IN Shanahan-Pendergast, Elisabeth

PA Ire.

SO PCT Int. Appl., 68 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002053138	A2	20020711	WO 2002-IE1	20020102
	WO 2002053138	A3	20020919		
	W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD, UA, UG, US, VN, YU, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG				
	EP 1351678	A2	20031015	EP 2002-727007	20020102
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	US 2004092583	A1	20040513	US 2004-250535	20040102
PRAI	IE 2001-2	A	20010102		
	WO 2002-IE1	W	20020102		

OS MARPAT 137:88442

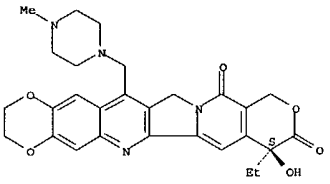
IT **149882-10-0**, Lurtotecan
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical formulation further including; incensole and furanogermacrens and compds. as antitumor and antimicrobial agents)

RN 149882-10-0 CAPLUS

CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L15 ANSWER 23 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L15 ANSWER 24 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB Camptothecin (CPT) compds. specifically acting on DNA topoisomerase I (TopoI) are promising antitumor drugs, and have been widely used in the clinic. In order to elucidate the model of action of camptothecin with TopoI-DNA complex, especially the contribution of A ring to antitumor activity, 21 compds. were built on the basis of the pharmacophoric conformation of camptothecin, which was determined from the previous conformational anal. and docking studies. 36 Structural and physicochem. descriptors consist of quantum chemical parameter calculated by AM1 method, hydrophobic parameter (MlogP) and mol. steric descriptors. The descriptors were examined using genetic algorithm (GA) and partial least squares (PLS) anal., the resulting QSAR models were of not only statistical significance, but also predictive ability. It has been indicated that substitution of electrophilic group on ring A of camptothecin will increase activity, especially on the C9. Our studies have also shown that the energy of HOMO (HOMO) was important for antitumor activity, which was due to the formation of π-κ charge transfer complex between camptothecin and TopoI-DNA complex disclosed by quantum chemical research. The understanding of mechanism of action of CPT with TopoI-DNA complex will benefit future design of novel potent antitumor camptothecin derivs.

AN 2002:494523 CAPLUS

DN 138:49385

TI Quantitative structure-activity relationships of antitumor camptothecin derivatives using quantum chemical methods and GA-PLS

AU Song, Yun-long; Zhang, Wan-nian; Ji, Hai-tao; Sheng, Chun-quan; Zhou, You-jun; Zhu, Ju; Lu, Jia-guo

CS School of Pharmacy, Second Military Medical University, Shanghai, 20043, Peop. Rep. China

SO Jisuanji Yu Yingyong Huaxue (2002), 19(1/2), 4-8, 18
CODEN: JYYHE6; ISSN: 1001-4160

PB Jisuanji Yu Yingyong Huaxue Bianjibu

DT Journal

LA Chinese

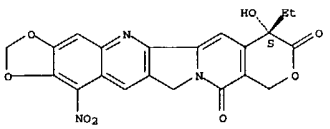
IT **135014-20-9**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(studies on quant. structure-activity relationships of antitumor camptothecin derivs. using quantum chemical methods and GA-PLS)

RN 135014-20-9 CAPLUS

CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L15 ANSWER 24 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L15 ANSWER 25 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The title compound I (R1, R2 = NO2, NH2, H, F, Cl, Br, I, COOH, OH, O-C1-6-alkyl, SH, S-C1-6-alkyl, CN, NH-C1-6-alkyl, N(C1-6-alkyl)2, CHO, C1-8-alkyl, N3, -Z-(CH2)a-N-((CH2)bOH)2, -Z(CH2)a-N(C1-6 alkyl)2; Z = O, NH, S; a,b = 2,3; CH2NR4R5; R4, R5 = H, C1-6-alkyl, C3-7- cycloalkyl, C3-7-cycloalkyl-C1-6-alkyl, C2-6-alkenyl, hydroxy-C1-6-alkyl, C1-6-alkoxy, COR6; R6 = H, C1-6-alkyl, perhalo-C1-6-alkyl, C3-7-cycloalkyl, C2-6-alkenyl, hydroxy-C1-6-alkyl, C1-6-alkoxy, C1-6-alkoxy-C1-6 alkyl, R4R5N = saturated 3-7 membered ring which may contain an O, S, NR7; R7 = H, C1-6-alkyl, perhalo-C1-6-alkyl, -aryl, -substituted aryl; R3 = H, or R2R3 combine to form a ring; R11 = H, C(O)-(CH2)m-NR12R13, -C(O)CHR14NR12R13; m = 1-6; R14 = amino acid side chain; R12, R13 = H, C1-8-alkyl or -C(O)CHR15NR16R17; R15 = amino acid side chain; R16, R17 = H, C1-8-alkyl; R18 = OR19, R19C(O)-(CH2)m-NR20, R21OC(O)CHR22NR20; R19 = H, C1-6-alkyl; m = 1-6; R22 = amino acid side chain; R20 = H, C1-8-alkyl, C(O)CHR23NR24R25; R23 = amino acid side chain; R24, R25 = H, C1-8 alkyl; R26 = C(O)(CH2)2C(COOR27)NH2; R27 = H or C1-6-alkyl; X = S, O) were prepared as antitumor agents, topoisomerase I inhibitors and agents to enhance the stability of the DNA topoisomerase I-DNA cleavable complex. Thus, 7-chloromethyl-10,11-methylenedioxy-20(S)-camptothecin was treated with glutathione to yield II. II showed activity as a topoisomerase I inhibitor and the ability to stabilize the DNA topoisomerase I-DNA cleavable complex. II had an IC50 of 20 nM when tested against the U937 human leukemia cell line.

AN 2002:391553 CAPLUS

DN 136:401911

TI Preparation of camptothecin conjugates containing a sulfhydryl group at the 7 position

IN Gamcsik, Michael P.; Adams, David J.; Colvin, O. Michael; Wall, Monroe E.; Wani, Mansukh C.; Manikumar, Govindarajan; Pommier, Yves

PA Research Triangle Institute, USA; Duke University; National Institutes of Health

SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002040040	A1	20020523	WO 2001-US42951	20011116

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002017767	A5	20020527	AU 2002-17767	20011116
EP 1351695	A1	20031015	EP 2001-996386	20011116

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

PRAI US 2000-712912 A 20001116
WO 2001-US42951 W 20011116

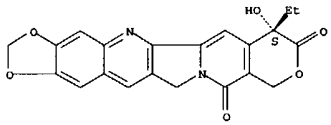
OS MARPAT 136:401911

IT **135415-73-5**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of camptothecin conjugates containing a sulfhydryl group as antitumor agents and topoisomerase I inhibitors)

RN 135415-73-5 CAPLUS

CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 26 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB Population pharmacokinetic-dynamic anal. was prospectively integrated in a broad phase II program of lurtotecan (GI147211), a novel camptothecin derived topoisomerase I inhibitor, to determine the population pharmacokinetic profile in a larger population, to estimate individual pharmacokinetic parameters and to investigate relationships with clin. outcome. A sparse sampling method was applied during course one, which involved two sampling time-points. A Bayesian algorithm was used to estimate individual pharmacokinetic parameters, in particular total plasma clearance (CL) and volume of distribution. In total, samples were collected of 109 (63%) of 173 patients. Pharmacokinetic-dynamic evaluation could be carried out successfully in 85 (78%) of the sampled patients. CL of lurtotecan showed substantial variability (mean 87±28 L/h) and was of the same magnitude as in the phase I studies where full pharmacokinetic curves were used. Residual variability in the population estimate of CL was 9.9%. No significant relationships were observed between exposure parameters and toxicity nor likelihood of tumor response, however the latter relationship may well have been obscured by the heterogeneity of the studied population. Prospective implementation of large scale population pharmacokinetic-dynamic anal. is feasible and important to establish whether interpatient variability in drug exposure is a major determinant of toxicity or activity.

AN 2002:328671 CAPLUS

DN 136:395294

TI Population pharmacokinetic and dynamic analysis of the topoisomerase I inhibitor lurtotecan in phase II studies

AU Schellens, J. H. M.; Heinrich, B.; Lehnert, M.; Gore, M. E.; Kaye, S. B.; Dombernowsky, P.; Paridaens, R.; van Oosterom, A. T.; Verweij, J.; Loos, W. J.; Calvert, H.; Pavlidis, N.; Cortes-Funes, H.; Wanders, J.; Roelvink, M.; Sessa, C.; Selinger, K.; Wissel, P. S.; Gamucci, T.; Hanauske, A. R.

CS The Netherlands Cancer Institute, Amsterdam, Neth.

SO Investigational New Drugs (2002), 20(1), 83-93
CODEN: INNDDK; ISSN: 0167-6997

PB Kluwer Academic Publishers

DT Journal

LA English

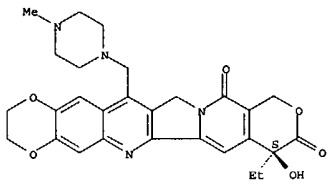
IT **149882-10-0**, Lurtotecan
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(population pharmacokinetic and dynamic anal. of topoisomerase I inhibitor lurtotecan in humans)

RN 149882-10-0 CAPLUS

CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L15 ANSWER 26 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 27 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB An addnl. chromatog. peak was observed in plasma samples of patients receiving NX 211, a liposomal formulation of the topoisomerase I inhibitor lurtotecan. The authors have isolated and purified this product by sequential solid-phase extns., and the authors report its structure and cytotoxicity relative to lurtotecan and related agents. NMR data indicate that cleavage of the piperazino moiety occurred at the N-C bond of the B-ring, yielding 7-methyl-10,11-ethylenedioxy-20(S)-camptothecin (MEC). Tests of the growth inhibition potential of MEC in 7 human tumor cell lines showed that the compound was approx. 2 - 18-fold more cytotoxic than lurtotecan, topotecan, and 7-ethyl-10-hydroxy-20(S)-camptothecin (SN-38). Subsequently, the authors found that MEC was the product of rapid photolysis of lurtotecan, with the rate of degradation inversely proportional to NX 211 concns., and greatly depends on light intensity. Furthermore, MEC concns. were found to increase significantly in plasma samples exposed to laboratory light but not in blood. MEC was not produced from NX 211 in the presence of human liver microsomes, suggesting that it is not a product of cytochrome P 450 metabolism Using a validated anal. method, trace levels of MEC were quantitated in blood samples of 2 patients. These observations confirm that the precautions for protection from light currently specified for preparation and administration of NX 211 dose solns. are critical Procedures to minimize formation of MEC, by the use of amber vials for NX 211 and by preparation of dilns. immediately before clin. use in a fashion completely protected from light, are now being routinely implemented.

AN 2002:277979 CAPLUS

DN 137:288476

TI Structural identification and biological activity of 7-methyl-10,11-ethylenedioxy-20(S)-camptothecin, a photodegradant of lurtotecan

AU Loos, Walter J.; Verweij, Jaap; Kehrer, Diederik F. S.; De Bruijn, Peter; De Groot, Franciscus M. H.; Hamilton, Marta; Nooter, Kees; Stoter, Gerrit; Sparreboom, Alex

CS Department of Medical Oncology, Rotterdam Cancer Institute, Rotterdam, 3075 EA, Neth.

SO Clinical Cancer Research (2002), 8(3), 856-862
CODEN: CCREP4; ISSN: 1078-0432

PB American Association for Cancer Research

DT Journal

LA English

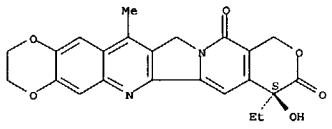
IT **191530-39-9**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); PYP (Physical process); BIOL (Biological study); PROC (Process)
(structural identification and biol. activity of 7-methyl-10,11-ethylenedioxy-20(S)-camptothecin, a photodegradant of lurtotecan)

RN 191530-39-9 CAPLUS

CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-methyl-, (8S)- (9CI)

L15 ANSWER 27 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 28 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB The present invention relates to an administration schedule comprising the i.v. administration of a α-halogen-acryloyl distamycin derivative, or a pharmaceutically acceptable salt thereof. The above administration allows the treatment of a variety of tumors in mammals. N-{5-[[[5-[[[5-[[[2-[[amino(imino)methyl]amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride was administered by i.v. infusion to patients with solid tumors.

AN 2002:275788 CAPLUS

DN 136:304046

TI Antitumor therapy comprising distamycin derivatives

IN Fowst, Camilla; Vreeland, Franzanne; Geroni, Maria Cristina Rosa

PA Pharmacia & Upjohn S.P.A., Italy; Pharmacia & Upjohn Company

SO PCT Int. Appl., 13 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002028389	A1	20020411	WO 2001-EP10988	20010921
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 6576612	B1	20030610	US 2000-676770	20001002
	AU 2002021622	A5	20020415	AU 2002-21622	20010921
	EE 200300129	A	20030616	EE 2003-129	20010921
	EP 1345604	A1	20030924	EP 2001-986259	20010921
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
	BR 2001014389	A	20040203	BR 2001-14389	20010921
	JP 2004510734	T2	20040408	JP 2002-532214	20010921
	NO 2003001410	A	20030327	NO 2003-1410	20030327
	US 2004006023	A1	20040108	US 2003-381272	20030624
PRAI	US 2000-676770	A	20001002		
	WO 2001-EP10988	W	20010921		

OS MARPAT 136:304046

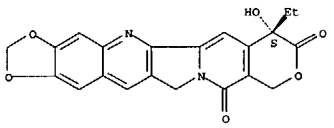
IT **135415-73-5**, 10,11-Methylenedioxycamptothecin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in combination with; antitumor therapy comprising distamycin derivs.)

RN 135415-73-5 CAPLUS

CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L15 ANSWER 28 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 29 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB The aim of this study was to determine the maximum-tolerated and recommended dose, toxicity profile, and pharmacokinetics of the liposomal topoisomerase I inhibitor lurtotecan (NX 211) administered as a 30-min i.v. infusion once every 3 wk in cancer patients. NX 211 was administered by peripheral infusion. Dose escalation decisions were based on all toxicities during the first cycle as well as pharmacokinetic parameters. Serial plasma, whole blood, and urine samples were collected for up to 96 h after the end of infusion, and drug levels were determined by high-performance liquid chromatog. Twenty-nine patients (16 women; median age, 56 yr; range, 39 to 74 yr) received 77 courses of NX 211 at dose levels of 0.4 (n = 3), 0.8 (n = 6), 1.6 (n = 3), 3.2 (n = 6), 3.8 (n = 6), and 4.3 mg/m2 (n = 5). Neutropenia and thrombocytopenia were the dose-limiting toxicities and were not cumulative. Other toxicities were mild to moderate. Nine patients had stable disease while undergoing treatment. The systemic clearance of lurtotecan in plasma and whole blood was 0.82±0.78 L/h/m2 and 1.15±0.96 L/h/m2, resp. Urinary recovery (Fu) of lurtotecan was 10.1% ± 4.05% (range, 4.9% to 18.9%). In contrast to systemic exposure measures, the dose excreted in urine (ie, dose × Fu) was significantly related to the percent decrease in neutrophil and platelet counts at nadir (P <.00001). The dose-limiting toxicities of NX 211 are neutropenia and thrombocytopenia. The recommended dose for phase II studies is 3.8 mg/m2 once every 3 wk. Pharmacol. data suggest a relationship between exposure to lurtotecan and NX 211-induced clin. effects.

AN 2002:241585 CAPLUS

DN 136:350104

TI Phase I and pharmacologic study of liposomal lurtotecan, NX 211: Urinary excretion predicts hematologic toxicity

AU Kehrer, Diederik F. S.; Bos, Annelies M.; Verweij, Jaap; Groen, Harry J.; Loos, Walter J.; Sparreboom, Alex; de Jonge, Maja J. A.; Hamilton, Marta; Cameron, Terri; de Vries, Elisabeth G. E.

CS Department of Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital, Rotterdam, 3075 EA, Neth.

SO Journal of Clinical Oncology (2002), 20(5), 1222-1231
CODEN: JCONDN; ISSN: 0732-183X

PB Lippincott Williams & Wilkins

DT Journal

LA English

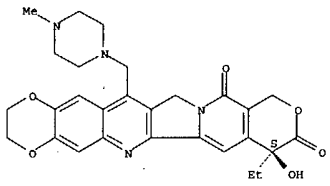
IT **149882-10-0**, NX 211
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lurtotecan, NX211, pharmacol. study results including prediction of hematol. toxicity based on urinary excretion)

RN 149882-10-0 CAPLUS

CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-[(4-methyl-1-piperazinyl)methyl]-, (8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

L15 ANSWER 29 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L15 ANSWER 30 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN

AB An improved camptothecin composition is provided for treating a patient having a disease associated with undesired cell growth or proliferation, including for example cancer. More particularly, the present invention is directed to a composition comprising camptothecin or a camptothecin-related compound and a DNA polymerase σ inhibitor.

AN 2002:107122 CAPLUS

DN 136:161336

TI Proliferation-inhibiting compositions containing an inhibitor of DNA polymerase σ and camptothecin or a related compound

IN Christman, Michael; Hecht, Sidney M.; Adams, Carrie; Wang, Zhenghe

PA University of Virginia Patent Foundation, USA

SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002009720	A1	20020207	WO 2001-US23908	20010731
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004029906	A1	20040212	US 2003-343563	20030807
PRAI	US 2000-222263P	P	20000731		
	WO 2001-US23908	W	20010731		

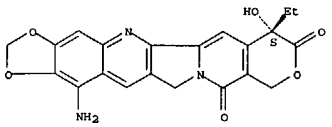
IT **135014-21-0**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(proliferation-inhibiting compns. containing inhibitor of DNA polymerase σ and camptothecin or related compound)

RN 135014-21-0 CAPLUS

CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L15 ANSWER 30 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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LAST RELOADED: Jun 18, 2004 (20040618/UP).

=> d 160-166
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L15 ANSWER 160 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:536473 CAPLUS
DN 115:136473
TI Preparation of 10,11-methylenedioxy-20(RS)-camptothecin and 10,11-methylenedioxy-20(S)-camptothecin analogs as antitumor agents
IN Wall, Monroe E.; Nicholas, Allan W.; Manikumar, Govindarajan; Wani, Mansukh C.
PA Research Triangle Institute, USA
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 418099	A2	19910320	EP 1990-310085	19900914
	EP 418099	A3	19920115		
	EP 418099	B1	20011219		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 5049668	A	19910917	US 1989-407749	19890915
	US 5180722	A	19930119	US 1990-581916	19900913
	ZA 9007360	A	19910731	ZA 1990-7360	19900914
	AT 211142	E	20020115	AT 1990-310085	19900914
	ES 2165346	T3	20020316	ES 1990-310085	19900914
	CA 2066780	AA	19910316	CA 1990-2066780	19900917
	CA 2066780	C	20020402		
PRAI	US 1989-407749	A	19890915		
	US 1990-581916	A	19900913		
	US 1987-38157	B1	19870414		
	US 1989-407779	A2	19890915		
	US 1990-511953	A2	19900417		

OS MARPAT 115:136473

L15 ANSWER 161 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1991:492686 CAPLUS
DN 115:92686
TI Camptothecin analogs as potent inhibitors of human colorectal cancer
IN Wall, Monroe E.; Wani, Mansukh
PA Research Triangle Institute, USA
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9105556	A1	19910502	WO 1990-US5986	19901023
	W: AU, CA, FI, HU, JP, KR, SU				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, NL, SE				
	US 5106742	A	19920421	US 1989-424910	19891023
	US 5244903	A	19930914	US 1990-600825	19901022
	CA 2067491	AA	19910424	CA 1990-2067491	19901023
	ZA 9008479	A	19911127	ZA 1990-8479	19901023
	EP 497910	A1	19920812	EP 1990-917526	19901023
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	JP 05508619	T2	19931202	JP 1991-500409	19901023
	AU 652728	B2	19940908	AU 1991-68866	19901023
PRAI	US 1989-424910	A	19891023		
	US 1990-600825		19901022		
	US 1987-32449	A2	19870331		
	US 1987-38157	A1	19870414		
	US 1990-511953	A2	19900417		
	WO 1990-US5986	W	19901023		

OS CASREACT 115:92686; MARPAT 115:92686

L15 ANSWER 162 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:611961 CAPLUS
DN 113:211961
TI Synthesis of camptothecin and its analogs as antitumor agents
IN Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindarajan
PA Research Triangle Institute, USA
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9003169	A1	19900405	WO 1989-US4176	19890928
	W: AU, DK, JP, KR, NO				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	US 4981968	A	19910101	US 1988-250094	19880928
	AU 8944187	A1	19900418	AU 1989-44187	19890928
	EP 436653	A1	19910717	EP 1989-911645	19890928
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
PRAI	US 1988-250094	A	19880928		
	US 1987-32449	A2	19870331		
	WO 1989-US4176	A	19890928		

OS MARPAT 113:211961

L15 ANSWER 163 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1990:48275 CAPLUS
DN 112:48275
TI DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogs [Erratum to document cited in CA111(17):146287f]
AU Hsiang, Yaw Huei; Liu, Leroy F.; Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindar; Kirschenbaum, Stanley; Silber, Robert; Potmesil, Milan
CS Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SO Cancer Research (1989), 49(23), 6868
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L15 ANSWER 164 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:546287 CAPLUS
DN 111:146287
TI DNA topoisomerase I-mediated DNA cleavage and cytotoxicity of camptothecin analogs
AU Hsiang, Yaw Huei; Liu, Leroy F.; Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindar; Kirschenbaum, Stanley; Silber, Robert; Potmesil, Milan
CS Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SO Cancer Research (1989), 49(16), 4385-9
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L15 ANSWER 165 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1989:205065 CAPLUS
DN 110:205065
TI Structure-activity study of the actions of camptothecin derivatives on mammalian topoisomerase I: evidence for a specific receptor site and a relation to antitumor activity
AU Jaxel, Christine; Kohn, Kurt W.; Wani, Mansukh C.; Wall, Monroe E.; Pommier, Yves
CS Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Research (1989), 49(6), 1465-9
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English

L15 ANSWER 166 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1987:33362 CAPLUS
DN 106:33362
TI Plant antitumor agents. 23. Synthesis and antileukemic activity of camptothecin analogs
AU Wani, Mansukh C.; Nicholas, Allan W.; Wall, Monroe E.
CS Research Triangle Inst., Research Triangle Park, NC, 27709, USA
SO Journal of Medicinal Chemistry (1986), 29(11), 2358-63
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
OS CASREACT 106:33362

6/24/04

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=> d abs bib fhitstr  150-159
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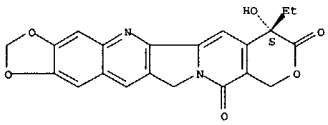
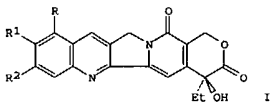
L15 ANSWER 150 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB In an effort to further extend the number of targets for development of antiretroviral agents, we have used an in vitro integrase assay to investigate a variety of chems., including topoisomerase inhibitors, antimalarial agents, DNA binders, naphthoquinones, the flavone quercetin, and caffeic acid phenethyl ester as potential human immunodeficiency virus type 1 integrase inhibitors. Our results show that although several topoisomerase inhibitors-including doxorubicin, mitoxantrone, ellipticines, and quercetin-are potent integrase inhibitors, other topoisomerase inhibitors-such as amsacrine, etoposide, teniposide, and camptothecin-are inactive. Other intercalators, such as chloroquine and the bifunctional intercalator ditercalinium, are also active. However, DNA binding does not correlate closely with integrase inhibition. The intercalator 9-aminoacridine and the polyamine DNA minor-groove binders spermine, spermidine, and distamycin have no effect, whereas the non-DNA binders primaquine, 5,8-dihydrox-1,4-naphthoquinone, and caffeic acid phenethyl ester inhibit the integrase. Caffeic acid phenethyl ester was the only compound that inhibited the integration step to a substantially greater degree than the initial cleavage step of the enzyme. A model of 5,8-dihydroxy-1,4-naphthoquinone interaction with the zinc finger region of the retroviral integrase protein is proposed.
AN 1993:440309 CAPLUS
DN 119:40309
TI Inhibitors of human immunodeficiency virus integrase
AU Pesen, Mark R.; Kohn, Kurt W.; Leteurtre, Francois; Pommier, Yves
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1993), 90(6), 2399-403
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
IT **135415-73-5**
RL: BIOL (Biological study)
(human immunodeficiency virus integrase inhibition and DNA binding by, antiretroviral activity in relation to)
RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L15 ANSWER 151 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI

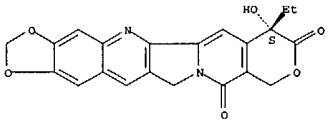


I

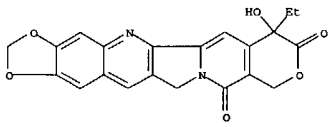
AB Quant. rate and equilibrium consts. for the hydrolysis of the lactone ring in camptothecin and analogs I (R-R2 = H; R = H, CH2NMe2, R1 = OH, R2 = H; R = NH2, R1, R2 = H; R = H, R1R2 = OCH2CH2O) at 25° in H2O were determined by high-performance liquid chromatog. with UV detection and by UV spectrophotometry. The lactone is converted to the carboxylate in a pH-dependent equilibrium No major differences between I were observed in rate and equilibrium consts., suggesting that the mechanism of lactone hydrolysis is independent of substitution on the A ring. The conversion of the lactone to its carboxylate form occurred under neutral and basic conditions and appeared to be largely dependent on hydroxide ion. The conversion of the carboxylate to the lactone was observed under neutral and acidic conditions and was pH-independent at pH >5 and dependent on hydronium ion at pH <5. Significant incorporation of 18O into the lactone ring of I (R = CH2NMe2, R1 = OH, R2 = H), a water-soluble analog of I (R-R2 = H), was observed during hydrolysis-recyclization in H2 18O. This finding strongly suggests that the mechanism of lactone ring hydrolysis involves acyl cleavage rather than alkyl cleavage. Kinetic solvent isotope effects for I (R-R2 = H) were used to speculate about the nature of the transition states involved in the opening and closing reactions of the lactone ring.
AN 1993:39234 CAPLUS
DN 118:39234
TI A kinetic and mechanistic study of the hydrolysis of camptothecin and some analogs
AU Fassberg, Julianne; Stella, Valentino J.
CS Dep. Pharm. Chem., Univ. Kansas, Lawrence, KS, 66045, USA
SO Journal of Pharmaceutical Sciences (1992), 81(7), 676-84
CODEN: JPMSAE; ISSN: 0022-3549
DT Journal
LA English
IT **135415-73-5**, 10,11-Methylenedioxycamptothecin
RL: RCT (Reactant); RACT (Reactant or reagent)
(lactone hydrolysis of, kinetics and mechanism of)
RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

L15 ANSWER 151 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

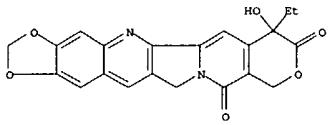
Absolute stereochemistry.



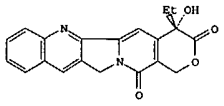
L15 ANSWER 152 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB The structure-activity relations of 30 camptothecin analogs as topoisomerase I inhibitors were studied. An assay based on the inhibition of DNA relaxation and the induction of DNA single-strand breaks by mouse leukemia L-1210 topoisomerase I enzyme was used.
AN 1992:523992 CAPLUS
DN 117:123992
TI Structure-activity relationship of topoisomerase I inhibition by camptothecin derivatives: evidence for the existence of a ternary complex
AU Pommier, Yves; Jaxel, Christine; Heise, Caroline R.; Kerrigan, Donna; Kohn, Kurt W.
CS Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, USA
SO DNA Topoisomerases Cancer (1991), 121-32. Editor(s): Potmesil, Milan; Kohn, Kurt W. Publisher: Oxford Univ. Press, New York, N. Y.
CODEN: 57RWAR
DT Conference
LA English
IT **104155-89-7**
RL: BIOL (Biological study)
(topoisomerase I inhibition by, ternary complex formation and structure in relation to)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



L15 ANSWER 153 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB A review with 38 refs. Drug development is needed to improve chemotherapy of patients with locally advanced or metastatic colon cancer and unfavorable prognosis. Topoisomerase I (topo I), a nuclear enzyme important for solving topol. problems arising during DNA replication and other cellular functions, has been identified as a principal target of a plant alkaloid, camptothecin, and its analogs prepared by total synthesis.
Significantly increased levels of topo I were found, compared to normal tissues, in advanced stages of colon cancer and in several other human malignancies. Presumably, high topo I levels in colon cancer and low levels in normal colon mucosa contribute to therapeutic efficacy of camptothecins. Two camptothecin analogs, 9-amino-20(RS) and 10,11-methylenedioxy-20(RS), were selected by tests with the purified topo
I and tissue-culture screens. Unlike other anticancer drugs, or parent camptothecin, both analogs induced long-term disease-free remissions, which resulted from single-agent treatment of human colon cancer xenograft
lines.
AN 1992:503369 CAPLUS
DN 117:103369
TI Preclinical studies of DNA topoisomerase I-targeted 9-amino and 10,11-methylenedioxy camptothecins
AU Potmesil, Milan; Giovanella, Beppino C.; Liu, Leroy F.; Wall, Monroe E.; Silber, Robert; Stehlin, John S.; Hsiang, Yaw Huei; Wani, Mansukh C.
CS Sch. Med., New York Univ., New York, NY, USA
SO DNA Topoisomerases Cancer (1991), 299-311. Editor(s): Potmesil, Milan; Kohn, Kurt W. Publisher: Oxford Univ. Press, New York, N. Y.
CODEN: 57RWAR
DT Conference; General Review
LA English
IT **104155-89-7**
RL: BIOL (Biological study)
(colon cancer of humans treatment with, DNA topoisomerase I in, in laboratory
animals)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



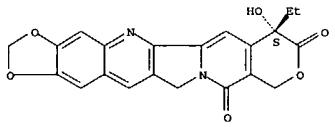
L15 ANSWER 154 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB 1H- and 13C spectra of camptothecin (I) 9- and 12-nitrocamptothecins, and 10,11-methylenedioxycamptothecin are assigned from 1D and 2D NMR data.
AN 1992:426853 CAPLUS
DN 117:26853
TI Proton- and carbon-13 and NMR spectra of camptothecin and derivatives
AU Ezell, Edward L.; Smith, Leland L.
CS Dep. Hum. Biol. Chem. Genet., Univ. Texas Med. Branch, Galveston, TX, 77550, USA
SO Journal of Natural Products (1991), 54(6), 1645-50
CODEN: JNPRDF; ISSN: 0163-3864
DT Journal
LA English
IT **135415-73-5**, 10,11-Methylenedioxycamptothecin
RL: PRP (Properties)
(carbon-13 NMR of)
RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

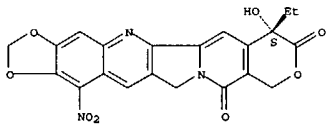
Absolute stereochemistry.



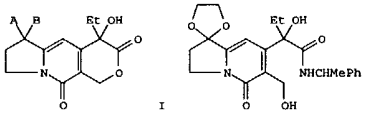
L15 ANSWER 155 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB In order to understand the high efficacy of camptothecin derivs. against human colon tumor xenografts in nude mice, the authors have studied the transport properties of camptothecin derivs. across cellular membranes of MDR1-overexpressing cells. MDR1 overexpression was shown to have little effect on camptothecin cytotoxicity; camptothecin was equally cytotoxic to
both the drug-sensitive parental cell line, KB 3-1, and its multidrug-resistant derivative, KBV1. The ability of camptothecin to overcome
MDR1-mediated resistance is most likely due to unimpaired accumulation of camptothecin in MDR1 cells as suggested from the following expts.: (a) cytotoxicity of camptothecin against KB V1 cells was not altered by the known MDR1-reversing agent, verapamil; (b) camptothecin was ineffective as
compared with vinblastine in competing with [3H]azidopine for photoaffinity labeling of MDR1; (c) camptothecin was equally efficient in trapping cellular topoisomerase I mols. on chromosomal DNA in the form of cleavable complexes in both KB 3-1 and KB V1 cells. The mechanism by which camptothecin overcomes MDR1-mediated resistance has been further studied using a number of uncharged and charged camptothecin derivs. In contrast to the uncharged camptothecin derivs., such as 9-amino-camptothecin and 10,11-methylenedioxy-camptothecin, the charged camptothecin derivative, topotecan, showed reduced cytotoxicity against MDR1-overexpressing KB V1 cells. The reduced cytotoxicity of topotecan in
KB V1 cells was due to the overexpression of MDR1 in KB V1 cells since verapamil restored both topotecan accumulation and cytotoxicity. These results suggest that the charge on camptothecin can affect the drug's sensitivity to MDR1. The possible effect of membrane permeability in determining drug selectivity of MDR1 is discussed.
AN 1992:75791 CAPLUS
DN 116:75791
TI Camptothecin overcomes MDR1-mediated resistance in human KB carcinoma cells
AU Chen, Allan Y.; Yu, Chiang; Potmesil, Milan; Wall, Monroe E.; Wani, Mansukh C.; Liu, Leroy F.
CS Dep. Biol. Chem., Johns Hopkins Sch. Med., Baltimore, MD, 21205, USA
SO Cancer Research (1991), 51(22), 6039-44
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
IT **135014-20-9**
RL: BIOL (Biological study)
(MDR1-mediated resistance in human carcinomas response to, mechanism of)
RN 135014-20-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L15 ANSWER 155 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L15 ANSWER 156 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I III

AB (R,S)-Lactone I (AB = OCH2CH2O) (II) was condensed with (R)-(+)-PhCHMeNH2 to give amides (S,R)-III and (R,R)-III which were separated by fractional crystallization from PhMe. The latter was hydrolyzed to give (R)-II and the ketal group cleaved to give (R)-I (AB = O). (S)-I (AB = O) (preparation given) was cyclocondensed with 2-(H2N)C6H4CHO to give 20(S)-camptothecin.
AN 1992:59712 CAPLUS
DN 116:59712
TI Preparation of 20(S)- and 20(R)-camptothecin derivatives
IN Wani, Mansukh C.; Nicholas, Allan W.; Wall, Monroe E.
PA Research Triangle Institute, USA
SO U.S., 10 pp. Cont. of U.S. Ser. No. 38,157, abandoned.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 6

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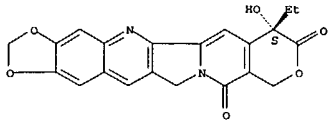
PI	US 5053512	A	19911001	US 1990-511953	19900417
	US 5180722	A	19930119	US 1990-581916	19900913
	US 5244903	A	19930914	US 1990-600825	19901022
	US 5122606	A	19920616	US 1991-666181	19910307
	US 5340817	A	19940823	US 1992-899865	19920617
	US 5364858	A	19941115	US 1992-986696	19921208
	US 5401747	A	19950328	US 1994-251368	19940531
PRAI	US 1987-38157	B1	19870414		
	US 1987-32449	A2	19870331		
	US 1989-407749	A2	19890915		
	US 1989-407779	A2	19890915		
	US 1989-424910	A2	19891023		
	US 1990-511953	A2	19900417		
	US 1990-581916	A1	19900913		
	US 1990-600825	A3	19901022		
	US 1992-986696	A1	19921208		

OS MARPAT 116:59712
IT **135415-73-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-

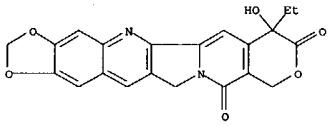
L15 ANSWER 156 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

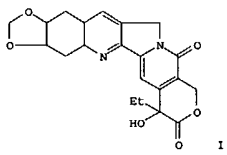


L15 ANSWER 157 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
AB Previous studies in rapidly proliferating rodent cells have suggested that the lethal effect of the DNA topoisomerase I inhibitor, camptothecin (CPT) is dependent upon the active participation of DNA replication. The purpose of the current study was to determine if this relation applies to more slowly growing human cells. In the present study, the human colon carcinoma cell line, HT-29 (45 h doubling time) was employed. Flow cytometric determination of S-phase cells either by S-phase fit model or rectangle fit model anal. predicted that 21% of exponentially growing HT-29 cells were undergoing DNA replication. These findings were confirmed by immunofluorescence microscopy of bromodeoxyuridine labeled cells. Based on these findings, the author expected only 20-30% of the cells to be susceptible to brief treatment (30 min) with CPT. Instead, 90-95% of HT-29 cells were killed. This apparent disparity was not due to prolonged cellular retention of drug after treatment because protein-linked DNA strand breaks reversed within 15 min of drug removal. Moreover, the DNA replication inhibitor, aphidicolin, fully protected HT-29 cells against CPT-induced killing but did not affect the production of CPT-induced protein-linked DNA strand breaks. Similar results were obtained with the CPT-analog, 10,11-methylenedioxycampothecin, which was 5-10-fold more potent than campothecin. These findings imply that replication events actively participate in HT-29 cell killing by the camptothecins and that CPT also exhibits actions outside of the processes of DNA elongation, presumably extending through most of G1 in HT-29 cells, where mol. events leading to DNA replication are initiated.
AN 1992:51009 CAPLUS
DN 116:51009
TI S-phase population analysis does not correlate with the cytotoxicity of camptothecin and 10,11-methylenedioxycamptothecin in human colon carcinoma HT-29 cells
AU O'Conner, Patrick M.; Nieves-Neira, Wilberto; Kerrigan, Donna; Bertrand, Richard; Goldman, Jonathan; Kohn, Kurt W.; Pommier, Yves
CS Lab. Mol. Pharmacol., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Communications (1991), 3(8), 233-40
CODEN: CNCMET; ISSN: 0955-3541
DT Journal
LA English
IT **104155-89-7**
RL: BIOL (Biological study)
(colon carcinoma of human inhibition by, DNA replication in relation to)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)

L15 ANSWER 157 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



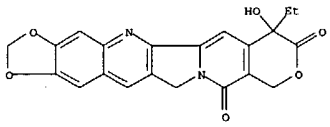
L15 ANSWER 158 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI



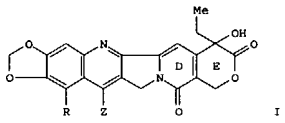
I

AB 10,11-Methylenedioxy-20-(RS)-camptothecin (MDO-CPT) (I) is a more potent inhibitor of purified DNA topoisomerase I than 20-(S)-camptothecin (CPT). The current studies compared the cytotoxicity and DNA damage induced by MDO-CPT and CPT in the human colon carcinoma cell line, HT-29. MDO-CPT was 7- to 10-fold more potent than CPT both for cytotoxicity (ID50 = 25 vs. 180 nM) and production of DNA single-strand breaks (SSB). Kinetics of SSB formation and reversal were similar for MDO-CPT and CPT. DNA-protein crosslinks (DPC) were also produced by both drugs with a SSB/DPC ratio of 1/1. Moreover, no SSB were detected under non-deproteinizing conditions, indicating that both CPT and MDO-CPT produced protein-linked DNA single-strand breaks. A good correlation between cytotoxic potency and protein-linked DNA single-strand break production was observed for CPT and MDO-CPT, implying a casual relationship between drug-induced cytotoxicity and topoisomerase I inhibition. The sensitivity of human colon HT-29 cancer cells to camptothecins may be a selective phenomenon since these cells normally express natural resistance to current chemotherapeutic drugs, including topoisomerase II inhibitors.
AN 1991:622898 CAPLUS
DN 115:222898
TI 10,11-Methylenedioxycamptothecin, a topoisomerase I inhibitor of increased potency: DNA damage and correlation to cytotoxicity in human colon carcinoma (HT-29) cells
AU O'Connor, Patrick M.; Kerrigan, Donna; Bertrand, Richard; Kohn, Kurt W.; Pommier, Yves
CS Div. Cancer Treat., Natl. Cancer Inst., Bethesda, MD, 20892, USA
SO Cancer Communications (1990), 2(12), 395-400
CODEN: CNCMET; ISSN: 0955-3541
DT Journal
LA English
IT **104155-89-7**
RL: PRP (Properties)
(cytotoxicity of, to human colon carcinoma cells, topoisomerase I inhibition and DNA damage in)
RN 104155-89-7 CAPLUS

L15 ANSWER 158 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



L15 ANSWER 159 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN
GI



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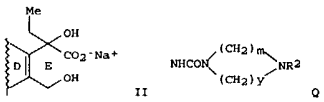

II Q

AB 10,11-Methylenedioxy (MDO) deriv. of camptothecin (CPT) alkaloids [I; Z = H, C1-8 alkyl; R = NO2, NH2, N3, H, halo, CO2H, HO, cyano, O, O-C1-3 alkyl, NH, SCH2CH2N(CH2CH2OH)2, NHCOCHR1NR2R3, Q, etc.; R1 = α-amino acid side chain; R2, R3 = H, alkyl; R3 = a peptide chain containing 1-3 amino acid units; m + y = 3-6, with a proviso], hydroxyacid derivs II, and their salts, were prepared Diazotization of 9-amino-10,11-MDO-20(S)-CPT by NaNO2 in the presence of H2SO4 gave diazonium sulfate salt which was treated with an excess H2PO2 at -10 to 0° to give title compound 10,11-MDO(S)-CPT (I; R = Z = H) (II). The latter in vitro inhibited topoisomerase I with EC50 of 0.01 μg/mL vs. 0.2 μg/mL for 20(S)-CPT as a control. II in vitro inhibited human colorectal tumor cell proliferation with IC50 = 0.003 μg/mL, vs. 0.02 μg/mL for 20(S)-CPT.
AN 1991:559504 CAPLUS
DN 115:159504
TI Preparation of camptothecin analogs as antitumor agents
IN Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindarajan
PA Research Triangle Institute, USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9104260	A2	19910404	WO 1990-US5172	19900917
	WO 9104260	A3	19910502		
	W: AU, CA, FI, HU, JP, KR, SU				
	AU 9063404	A1	19910418	AU 1990-63404	19900917
	AU 640950	B2	19930909		
	JP 05502017	T2	19930415	JP 1990-512782	19900917

L15 ANSWER 159 OF 166 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

	JP 3210329	B2	20010917	
	EP 538534	A1	19930428	EP 1991-402864 19911025
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE			
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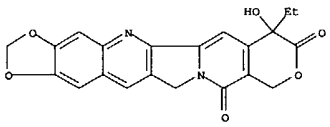
	US 1989-407749	A	19890915	
	US 1990-581916	A	19900913	
	WO 1990-US5172	A	19900917	

OS MARPAT 115:159504
IT **104155-89-7**
RL: PROC (Process)
(conversion of, to sodium salt, in preparation of antitumor agent)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



6/24/04

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DICTIONARY FILE UPDATES:  23 JUN 2004  HIGHEST RN 698346-19-9

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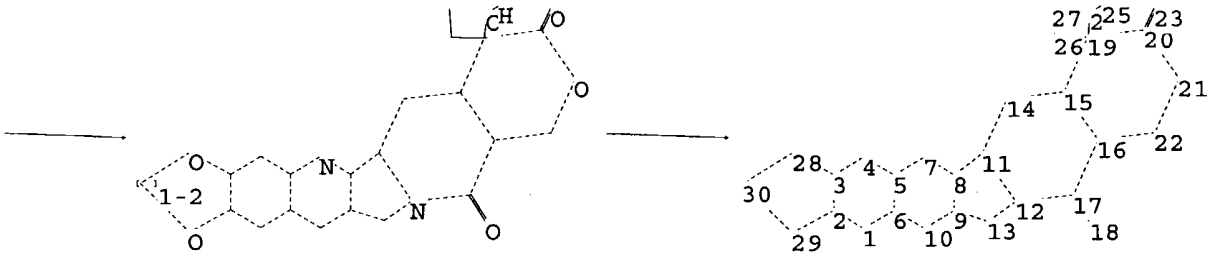

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L16 STR

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L17           1 SEA SSS SAM L16 (     2 REACTIONS)

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FULL SEARCH INITIATED 17:02:05 FILE 'CASREACT'
SCREENING COMPLETE - 41 REACTIONS TO VERIFY FROM 9 DOCUMENTS

100.0% DONE 41 VERIFIED 37 HIT RXNS 7 DOCS
SEARCH TIME: 00.00.01

L18 7 SEA SSS FUL L16 (37 REACTIONS)

=> d l18 all

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

AN 138:162968 CASREACT

TI Dual role of glutathione in modulating camptothecin activity: depletion potentiates activity, but conjugation enhances the stability of the topoisomerase I-DNA cleavage complex

AU Gamcsik, Michael P.; Kasibhatla, Mohit S.; Adams, David J.; Flowers, James L.; Colvin, O. Michael; Manikumar, Govindarajan; Wani, Mansukh; Wall, Monroe E.; Kohlhagen, Glenda; Pommier, Yves

CS Department of Medicine, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC, 27710, USA

SO Molecular Cancer Therapeutics (2001), 1(1), 11-20
CODEN: MCTOCF; ISSN: 1535-7163

PB American Association for Cancer Research

DT Journal

LA English

CC 1-3 (Pharmacology)

AB Depletion of glutathione (GSH) in MCF-7 and MDA-MB-231 cell lines by pretreatment with the GSH synthesis inhibitor buthionine sulfoximine potentiated the activity of 10,11-methylenedioxy-20(S)-camptothecin, SN-38 [7-ethyl-10-hydroxy-20(S)-camptothecin], topotecan, and 7-chloromethyl-10,11-methylenedioxy-20(S)-camptothecin (CMMDC). The greatest potentiation was observed with the alkylating camptothecin CMMDC. Buthionine sulfoximine pretreatment also increased the number of camptothecin-induced DNA-protein crosslinks, indicating that GSH affects the mechanism of action of camptothecin. We also report that GSH interacts with CMMDC to form a stable conjugate, 7-(glutathionylmethyl)-10,11-methylenedioxy-20(S)-camptothecin (GSMMDC), which is formed spontaneously in buffered solns. and in MCF-7 cells treated with CMMDC. GSMMDC was synthesized and found to be nearly as active as 10,11-methylenedioxy-20(S)-camptothecin in a topoisomerase (topo) I-mediated DNA nicking assay. The resulting topo I cleavage complexes were remarkably stable. In cell culture, GSMMDC displayed potent growth-inhibitory activity against U937 and P388 leukemia cell lines. GSMMDC was not active against a topo I-deficient P388 cell line, indicating that topo I is its cellular target. Peptide-truncated analogs of GSMMDC were prepared and evaluated. All three derivs. [7-(γ-glutamylcysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, 7-(cysteinylglycylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, and 7-(cysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin] displayed topo I and cell growth-inhibitory activity. These results suggest that 7-peptidyl derivs. represent a new class of camptothecin analogs.

ST glutathione camtothecin breast cancer leukemia topoisomerase DNA cleavage complex; synthesis camptothecin peptide analog MSBAR antitumor lactone ring

IT Mammary gland, neoplasm
(adenocarcinoma; synthesis and structure-activity relationship of camptothecin-peptide analogs)

IT Structure-activity relationship
(antitumor; glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)

IT DNA
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(complexes; glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT Alkylating agents, biological
Antitumor agents
Conjugation (bond)
Human
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT Leukemia
(synthesis and structure-activity relationship of camptothecin-peptide analogs)

IT 143180-75-0
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT 70-18-8, Glutathione, biological studies
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT 135415-73-5, 10,11-Methylenedioxy-20(S)-camptothecin
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT 7689-03-4, Camptothecin 86639-52-3, SN-38 149882-14-4 496926-01-3 496926-03-5 496926-04-6 496926-05-7
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glutathione modulation of camptothecin activity in breast cancer and leukemia: GSH depletion and conjugation enhancement of topoisomerase I-DNA cleavage complex stability)

IT 428816-97-1P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and structure-active relationship of camptothecin-peptide analogs)

IT 52-90-4, Cysteine, reactions 67-56-1, Methanol, reactions 636-58-8, γ-Glutamylcysteine 10035-10-6, Hydrobromic acid, reactions 19246-18-5, Cysteinyl-glycine
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and structure-active relationship of camptothecin-peptide analogs)

IT 191530-33-3P 428816-69-7P

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and structure-active relationship of camptothecin-peptide analogs)

IT 428816-84-6P 428817-20-3P 496925-96-3P 496926-00-2P
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and structure-activity relationship of camptothecin-peptide analogs)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Bom, D; J Med Chem 2000, V43, P3970 CAPLUS
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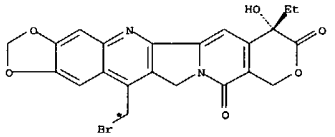
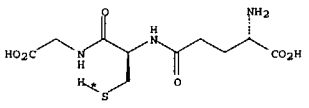
RX(1) OF 15 ...A + B ===> C

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



A



B

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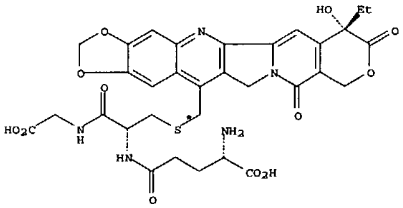


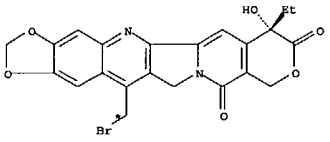
C

YIELD 88%

RX(1) RCT A 191530-33-3, B 70-18-8
PRO C 428816-84-6
SOL 7732-18-5 Water, 68-12-2 DMF

RX(2) OF 15 ...A + F ===> G

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



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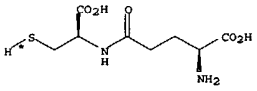

F

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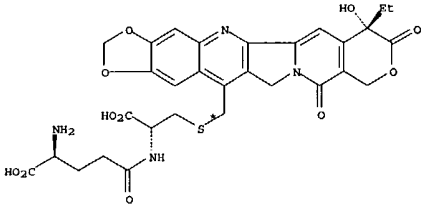
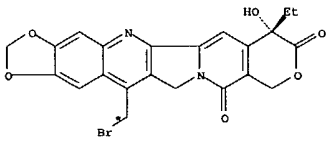


G
YIELD 86%

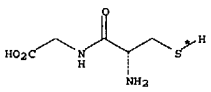
RX(2) RCT A 191530-33-3, F 636-58-8
PRO G **428817-20-3**
SOL 7732-18-5 Water, 68-12-2 DMF

RX(3) OF 15 ...A + H ===> I

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



A



H

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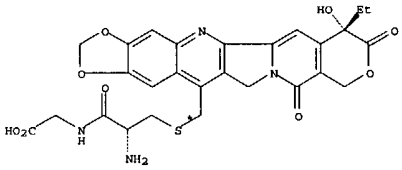
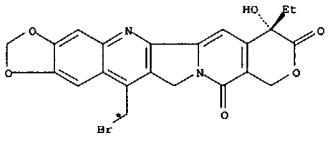


I
YIELD 82%

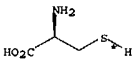
RX(3) RCT A 191530-33-3, H 19246-18-5
PRO I **496925-96-3**
SOL 7732-18-5 Water, 68-12-2 DMF

RX(4) OF 15 ...A + J ===> K

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



A



J

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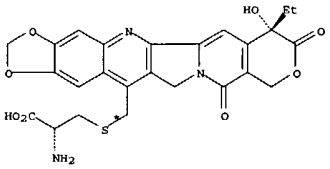
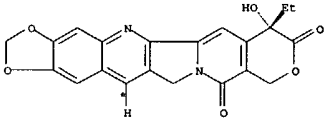


K
YIELD 91%

RX(4) RCT A 191530-33-3, J 52-90-4
PRO K **428816-97-1**
SOL 7732-18-5 Water, 68-12-2 DMF

RX(5) OF 15 L + M ===> N...

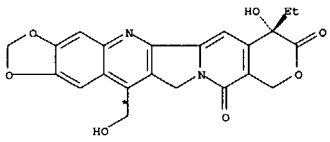


L

M

(5)

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



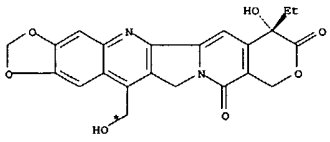
N
YIELD 77%

RX(5) RCT L 135415-73-5, M 67-56-1

STAGE(1)
RGT O 7664-93-9 H2SO4, P 7720-78-7 FeSO4, Q 7722-84-1 H2O2
SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)
SOL 7732-18-5 Water
PRO N **428816-69-7**

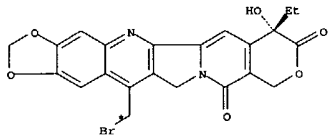
RX(6) OF 15 ...N ===> A...



N

(6)

L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN (Continued)



A
YIELD 78%

RX(6) RCT N 428816-69-7
RGT R 10035-10-6 HBr
PRO A **191530-33-3**
CAT 7664-93-9 H2SO4

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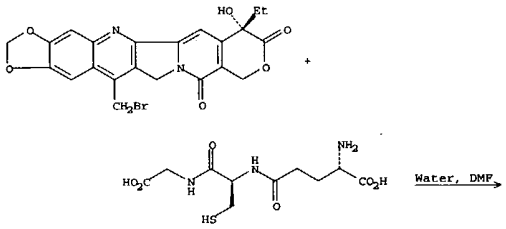
L18 ANSWER 1 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

RX(1) OF 15



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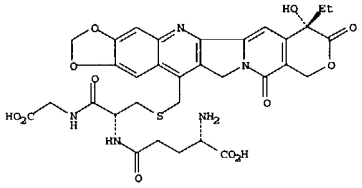

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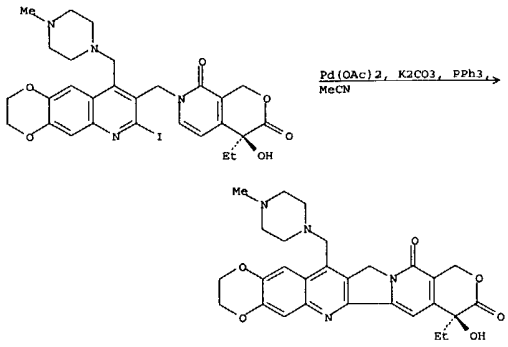
REF: Molecular Cancer Therapeutics, 1(1), 11-20; 2001

L18 ANSWER 2 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

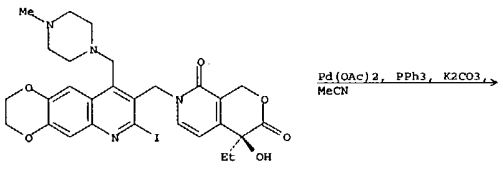
RX(1) OF 2



REF: U.S., 6063923, 16 May 2000

L18 ANSWER 3 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

RX(2) OF 2



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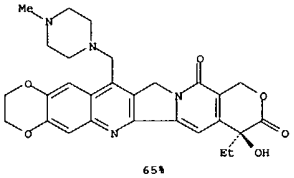

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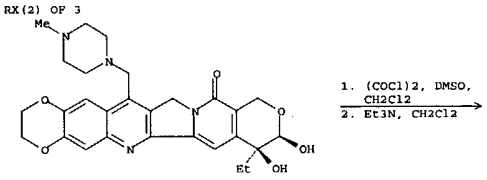
REF: Tetrahedron, 53(32), 10953-10970; 1997

L18 ANSWER 4 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

RX(2) OF 3



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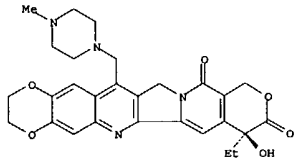
RX(2) OF 3



REF: PCT Int. Appl., 9716454, 09 May 1997

L18 ANSWER 5 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

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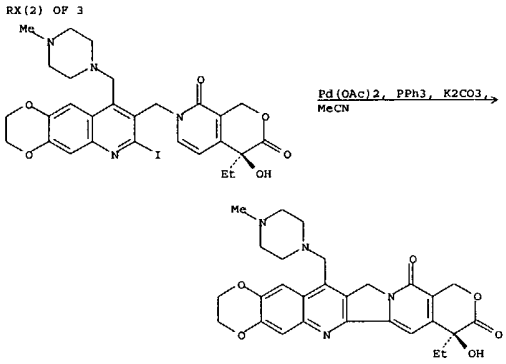

REF: PCT Int. Appl., 9529919, 09 Nov 1995

L18 ANSWER 6 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

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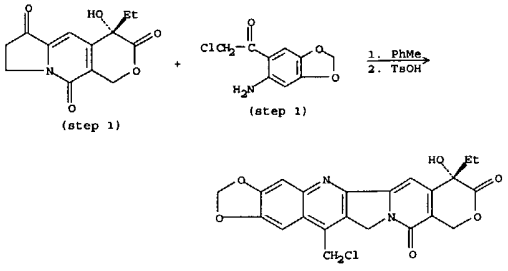

REF: Journal of Medicinal Chemistry, 38(3), 395-401; 1995
NOTE: KEY STEP

L18 ANSWER 7 OF 7 CASREACT COPYRIGHT 2004 ACS on STN

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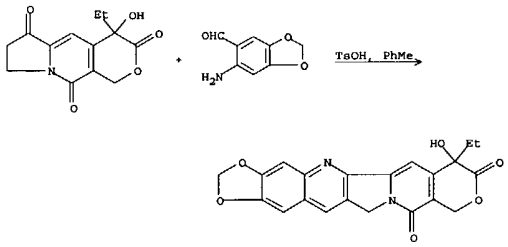

REF: Journal of Medicinal Chemistry, 29(11), 2358-63; 1986

6/24/04

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FULL ESTIMATED COST	130.36	872.15

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
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FILE 'HOME' ENTERED AT 17:04:31 ON 24 JUN 2004

=> file registry

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

FILE 'REGISTRY' ENTERED AT 17:04:43 ON 24 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 23 JUN 2004 HIGHEST RN 698346-19-9
DICTIONARY FILE UPDATES: 23 JUN 2004 HIGHEST RN 698346-19-9

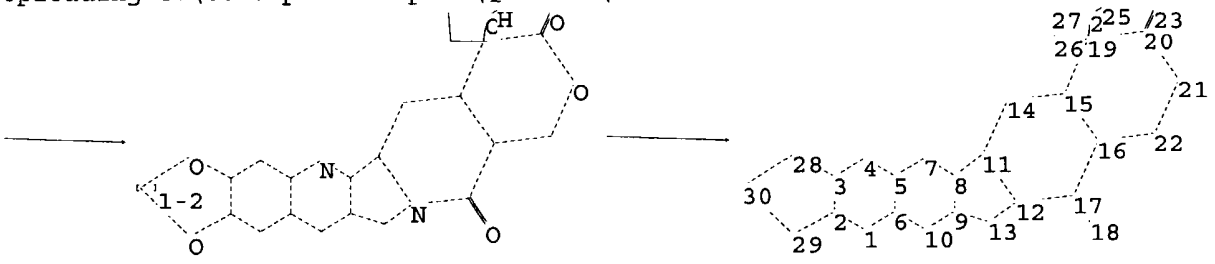
TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Stnexp4 corrupted\QUERIES\10606795.str



6/24/04

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chain nodes :
18  23  24  25  26  27
ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16  17  19  20  21  22  28  29
30
chain bonds :
17-18  19-24  19-26  20-23  24-25  26-27
ring bonds :
1-2  1-6  2-3  2-29  3-4  3-28  4-5  5-6  5-7  6-10  7-8  8-9  8-11  9-10  9-13
11-12  11-14  12-13  12-17  14-15  15-16  15-19  16-17  16-22  19-20  20-21  21-22
28-30  29-30
exact/norm bonds :
1-2  1-6  2-3  2-29  3-4  3-28  4-5  5-6  5-7  6-10  7-8  8-9  8-11  9-10  9-13
11-12  11-14  12-13  12-17  14-15  15-16  15-19  16-17  16-22  17-18  19-20  19-24
20-21  20-23  21-22  28-30  29-30
exact bonds :
19-26  24-25  26-27


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:Atom  18:CLASS  19:Atom
20:Atom  21:Atom  22:Atom  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS
28:Atom  29:Atom  30:Atom
fragments assigned product role:
containing 1



L1      STRUCTURE UPLOADED

=>  sl1
SL1 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> s l1
SAMPLE SEARCH INITIATED 17:05:05 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     30 TO ITERATE

100.0% PROCESSED      30 ITERATIONS                              21 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:          272 TO      928
PROJECTED ANSWERS:             146 TO      694

L2            21 SEA SSS SAM L1

=> s l1 ful
FULL SEARCH INITIATED 17:05:11 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -    534 TO ITERATE

100.0% PROCESSED     534 ITERATIONS                             356 ANSWERS
```

6/24/04

SEARCH TIME: 00.00.01

L3 356 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 155.42 155.63

FILE 'CAPLUS' ENTERED AT 17:05:23 ON 24 JUN 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 24 Jun 2004 VOL 140 ISS 26
FILE LAST UPDATED: 23 Jun 2004 (20040623/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3
L4 166 L3

=> s l3/p
L5 47 L3/P

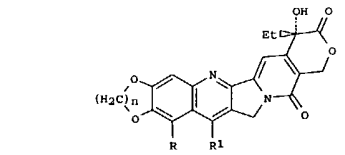
=> s l5 and amino cyano
982462 AMINO
42 AMINOS
982479 AMINO (AMINO OR AMINOS)
73963 CYANO
3 CYANOS
73964 CYANO (CYANO OR CYANOS)
633 AMINO CYANO (AMINO(W)CYANO)
L6 0 L5 AND AMINO CYANO

=> s l5 and cyano
73963 CYANO
3 CYANOS
73964 CYANO (CYANO OR CYANOS)
L7 4 L5 AND CYANO

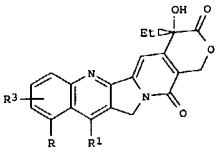
6/24/04

=> d abs bib hitstr 1-4

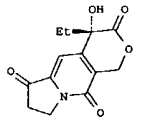
L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II



III

AB The camptothecin deriva. I (R = NO2, NH2, N3, H, halo, CO2H, OH, substituted alkyl, substituted amino, alkoxy, **cyano**, CH2R22, etc.; R1 = CH2R2, H, alkyl; R2 = functional group which is displaced by a nucleophilic group of DNA, n = 1, 2) and II (R3 = H, **cyano**, CHO, OH, amino, alkyl, etc.) were prepared as antitumor compds. I and II inhibit the enzyme topoisomerase I and alkylate DNA of associated topoisomerase I-DNA complexes (no data). Thus, 2-nitroacetophenone was treated with the tricyclic ketone III to give 7-methyl-20(S)-camptothecine, which was brominated with NBS to give 7-(bromomethyl)-20(S)-camptothecin.
AN 1997:457090 CAPLUS
DN 127:65987
TI Preparation of camptothecin derivatives with combined topoisomerase I inhibition and DNA alkylation properties
IN Wall, Monroe E.; Wani, Mansukh C.
PA Research Triangle Institute, USA
SO PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9719085	A1	19970529	WO 1996-US18282	19961122

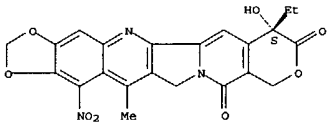
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK,

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9677329	A1	19970611	AU 1996-77329	19961122
US 5932588	A	19990803	US 1997-946701	19971008
US 5985888	A	19991116	US 1997-971694	19971117

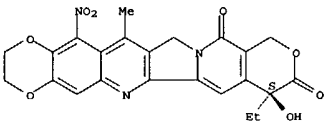
PRAI US 1995-561664 19951122
WO 1996-US18282 19961122
US 1997-946701 19971008
OS MARPAT 127:65987
IT **191530-75-3P 191530-77-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of camptothecin derivs. with combined topoisomerase I inhibition and DNA alkylation properties)
RN 191530-75-3 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-14-methyl-15-nitro-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191530-77-5 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 8-ethyl-2,3-dihydro-8-hydroxy-15-methyl-16-nitro-, (S)- (9CI) (CA INDEX NAME)

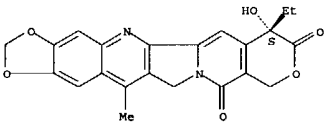
Absolute stereochemistry.



L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

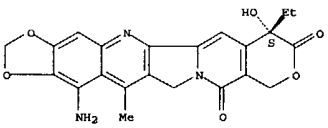
IT **172546-50-8P 191530-45-7P 191530-48-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of camptothecin derivs. with combined topoisomerase I inhibition and DNA alkylation properties)
RN 172546-50-8 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-14-methyl-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191530-45-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy-14-methyl-, (S)- (9CI) (CA INDEX NAME)

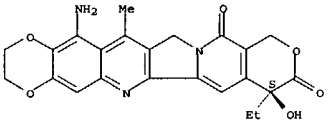
Absolute stereochemistry.



RN 191530-48-0 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 16-amino-8-ethyl-2,3-dihydro-8-hydroxy-15-methyl-, (S)- (9CI) (CA INDEX NAME)

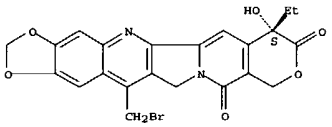
Absolute stereochemistry.

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



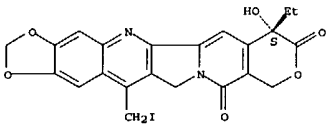
IT **191530-33-3P 191530-35-5P 191530-52-6P**
191530-54-8P 191530-93-5P 191530-94-6P
191532-16-8P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of camptothecin derivs. with combined topoisomerase I inhibition and DNA alkylation properties)
RN 191530-33-3 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 14-(bromomethyl)-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 191530-35-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-14-(iodomethyl)-, (S)- (9CI) (CA INDEX NAME)

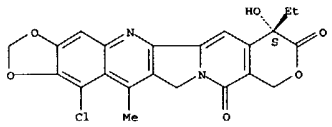
Absolute stereochemistry.



RN 191530-52-6 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-chloro-7-ethyl-7-hydroxy-14-methyl-, (S)- (9CI) (CA INDEX NAME)

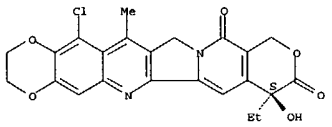
L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry.



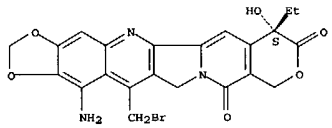
RN 191530-54-8 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 16-chloro-8-ethyl-2,3-dihydro-8-hydroxy-15-methyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



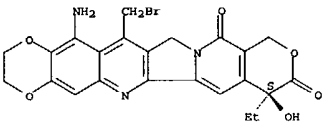
RN 191530-93-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-14-(bromomethyl)-7-ethyl-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



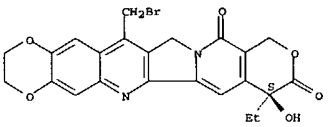
RN 191530-94-6 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 16-amino-15-(bromomethyl)-8-ethyl-2,3-dihydro-8-hydroxy-, (S)- (9CI) (CA INDEX NAME)

L7 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
Absolute stereochemistry.

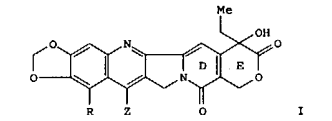


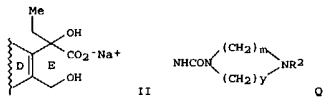
RN 191532-16-8 CAPLUS
CN 11H-1,4-Dioxino[2,3-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-9,12(8H,14H)-dione, 15-(bromomethyl)-8-ethyl-2,3-dihydro-8-hydroxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
GI





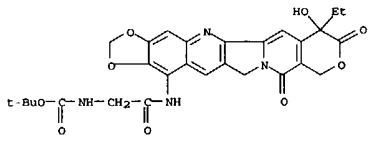
AB 10,11-Methylenedioxy (MDO) deriva. of camptothecin (CPT) alkaloids [I; Z = H, C1-8 alkyl; R = NO2, NH2, N3, H, halo, CO2H, HO, cyano, O, O-C1-3 alkyl, NH, SCH2CH2N(CH2CH2OH)2, NHCOCHR1NR2R3, Q, etc.; R1 = α-amino acid side chain; R2, R3 = H, alkyl; R3 = a peptide chain containing 1-3 amino acid units; m + y = 3-6, with a proviso], hydroxyacid
deriva II, and their salts, were prepared Diazotization of 9-amino-10,11-MDO-20(S)-CPT by NaNO2 in the presence of H2SO4 gave diazonium sulfate salt which was treated with an excess H2PO2 at -10 to 0° to give title compound 10,11-MDO(S)-CPT (I; R = Z = H) (II). The latter in vitro inhibited topoisomerase I with EC50 of 0.01 μg/mL vs. 0.2 μg/mL for 20(S)-CPT as a control. II in vitro inhibited human colorectal tumor cell proliferation with IC50 = 0.003 μg/mL, vs. 0.02 μg/mL for 20(S)-CPT.
AN 1991:559504 CAPLUS
DN 115:159504
TI Preparation of camptothecin analogs as antitumor agents
IN Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindarajan
PA Research Triangle Institute, USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
PAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9104260	A2	19910404	WO 1990-US5172	19900917
	WO 9104260	A3	19910502		
	W: AU, CA, FI, HU, JP, KR, SU				
	AU 9063404	A1	19910418	AU 1990-63404	19900917
	AU 640950	B2	19930909		
	JP 05502017	T2	19930415	JP 1990-512782	19900917
	JP 3210329	B2	20010917		

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

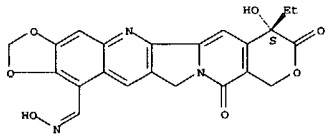
	EP 538534	A1	19930428	EP 1991-402864	19911025
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
PRAI	US 1989-407779	A	19890915		
	US 1989-407749	A	19890915		
	US 1990-581916	A	19900913		
	WO 1990-US5172	A	19900917		

OS MARPAT 115:159504
IT **136173-33-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of, in preparation of antitumor agent)
RN 136173-33-6 CAPLUS
CN Carbamic acid, [2-[(7-ethyl-7,8,11,13-tetrahydro-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)amino]-2-oxoethyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



IT **136094-54-7P 136094-55-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and hydrolysis of, in preparation of antitumor agent)
RN 136094-54-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-15-carboxaldehyde, 7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-, 15-oxime, (S)- (9CI) (CA INDEX NAME)

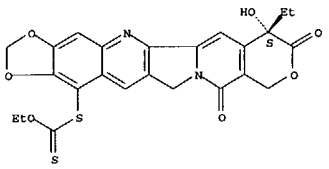
Absolute stereochemistry.
Double bond geometry unknown.



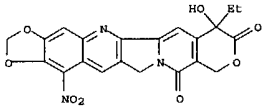
RN 136094-55-8 CAPLUS
CN Carbonodithioic acid, O-ethyl S-7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



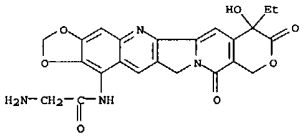
IT **135095-69-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reduction of, in preparation of antitumor agent)
RN 135095-69-1 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro- (9CI) (CA INDEX NAME)



IT **135014-20-9P 135014-22-1P 135014-26-5P**
135095-71-5P 135096-87-6P 135415-73-5P
136094-37-6P 136094-38-7P 136094-39-8P
136094-40-1P 136094-41-2P 136094-42-3P
136094-43-4P 136094-44-5P 136094-45-6P
136094-46-7P 136094-47-8P 136094-48-9P
136094-49-0P 136094-50-3P 136094-51-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antitumor agent)
RN 135014-20-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro-, (7S)- (9CI) (CA INDEX NAME)

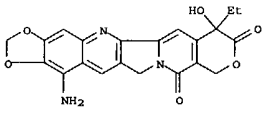
Absolute stereochemistry.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



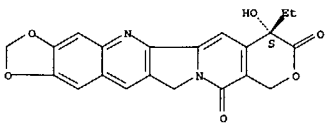
● HCl

RN 135096-87-6 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

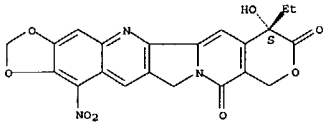
Absolute stereochemistry.



RN 136094-37-6 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-15-carboxylic acid, 7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-, (S)- (9CI) (CA INDEX NAME)

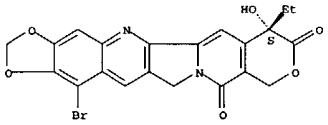
Absolute stereochemistry.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



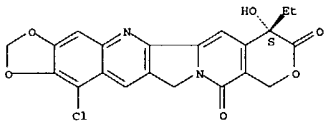
RN 135014-22-1 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-bromo-7-ethyl-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



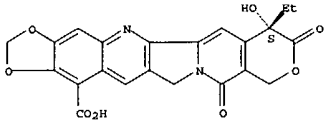
RN 135014-26-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-chloro-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



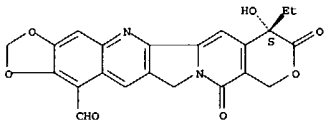
RN 135095-71-5 CAPLUS
CN Acetamide, 2-amino-N-(7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-, monohydrochloride (9CI) (CA INDEX NAME)

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



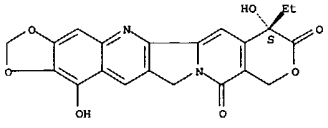
RN 136094-38-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-15-carboxaldehyde, 7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 136094-39-8 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7,15-dihydroxy-, (S)- (9CI) (CA INDEX NAME)

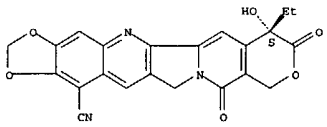
Absolute stereochemistry.



RN 136094-40-1 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-15-carbonitrile, 7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-, (S)- (9CI) (CA INDEX NAME)

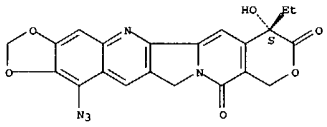
Absolute stereochemistry.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



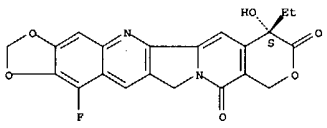
RN 136094-41-2 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-azido-7-ethyl-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 136094-42-3 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-15-fluoro-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

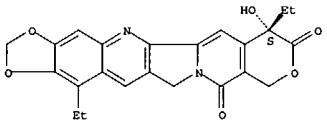
Absolute stereochemistry.



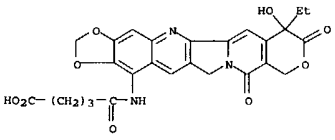
RN 136094-43-4 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-iodo-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

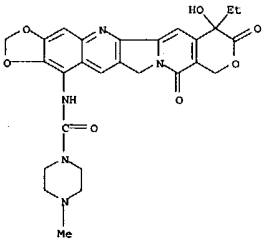
L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 136094-47-8 CAPLUS
CN Pentanoic acid,
5-[[7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl]amino]-5-oxo- (9CI) (CA INDEX NAME)

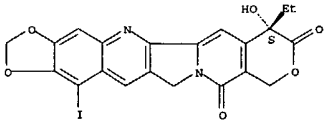


RN 136094-48-9 CAPLUS
CN 1-Piperazinecarboxamide, N-(7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-4-methyl- (9CI) (CA INDEX NAME)



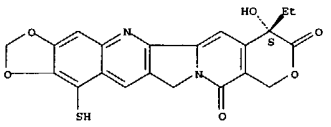
RN 136094-49-0 CAPLUS

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



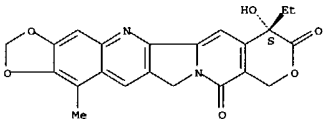
RN 136094-44-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-mercapto-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 136094-45-6 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-methyl-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

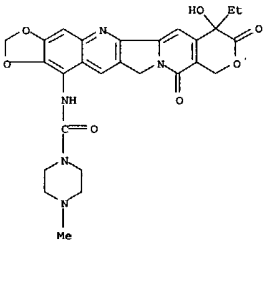


RN 136094-46-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7,15-diethyl-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

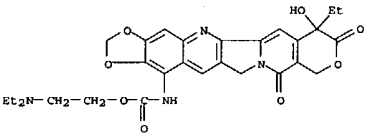
Absolute stereochemistry.

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

CN 1-Piperazinecarboxamide, N-(7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-4-methyl-, monohydrochloride (9CI) (CA INDEX NAME)

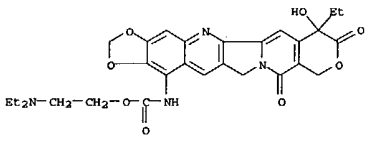


RN 136094-50-3 CAPLUS
CN Carbamic acid,
(7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-, 2-(diethylamino)ethyl ester (9CI) (CA INDEX NAME)



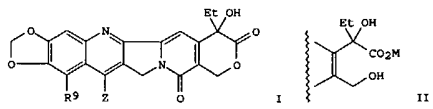
RN 136094-51-4 CAPLUS
CN Carbamic acid,
(7-ethyl-7,8,11,13-tetrahydro-7-hydroxy-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-, 2-(diethylamino)ethyl ester, monohydrochloride (9CI) (CA INDEX NAME)

L7 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● HCl

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
GI

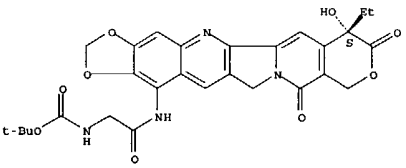


AB The title analogs, i.e. lactones I and ring-opened acid salts II (Z = H, alkyl; R = NO2, NH2, N3, H, halo, CO2H, OH, alkoxy, SH, alkylthio, **cyano**, CH2NH2, CHO, alkyl, acylamino, etc.; M = monovalent metal cation; both R and Z = H in I), were prepared Thus, nitration of 10,11-methylenedioxy-20(S)-camptothecin (III) with HNO3-H2SO4 gave 75% (crystallized) 9-nitro derivative, which was hydrogenated over Pd/C in EtOH to give 67% (crystallized) 9-amino derivative (IV). The EC50 of both III and IV for inhibition of topoisomerase I in the cleavable complex assay was .apprx.0.01 μg/mL, vs. .apprx.0.2 μg/mL for 20(S)-camptothecin (V). For III, IV, and V, the IC50 values for inhibition of [3H]-thymidine uptake into human colon tumor DNA were .apprx.0.003, .apprx.0.002, and .apprx.0.02 μg/mL, resp.
AN 1991:536473 CAPLUS
DN 115:136473
TI Preparation of 10,11-methylenedioxy-20(RS)-camptothecin and 10,11-methylenedioxy-20(S)-camptothecin analogs as antitumor agents
IN Wall, Monroe E.; Nicholas, Allan W.; Manikumar, Govindarajan; Wani, Mansukh C.
PA Research Triangle Institute, USA
SO Eur. Pat. Appl., 21 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	EP 418099	A2	19910320	EP 1990-310085	19900914
	EP 418099	A3	19920115		
	EP 418099	B1	20011219		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
	US 5049668	A	19910917	US 1989-407749	19890915
	US 5180722	A	19930119	US 1990-581916	19900913
	ZA 9007360	A	19910731	ZA 1990-7360	19900914
	AT 211142	E	20020115	AT 1990-310085	19900914
	ES 2165346	T3	20020316	ES 1990-310085	19900914
	CA 2066780	AA	19910316	CA 1990-2066780	19900917
	CA 2066780	C	20020402		
PRAI	US 1989-407749	A	19890915		

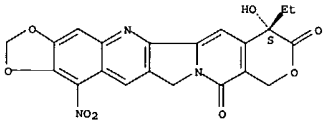
L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
US 1990-581916 A 19900913
US 1987-38157 B1 19870414
US 1989-407779 A2 19890915
US 1990-511953 A2 19900417
OS MARPAT 115:136473
IT **135014-27-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and deprotection of)
RN 135014-27-6 CAPLUS
CN Carbamic acid, [2-[(7-ethyl-7,8,11,13-tetrahydro-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)amino]-2-oxoethyl]-, 1,1-dimethylethyl ester, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **135014-20-9P 135014-21-0P 135014-22-1P**
135014-23-2P 135014-26-5P 135095-69-1P
135096-87-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antitumor agent)
RN 135014-20-9 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro-, (7S)- (9CI) (CA INDEX NAME)

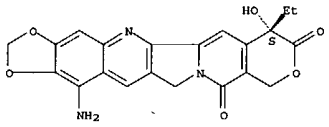
Absolute stereochemistry.



RN 135014-21-0 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX

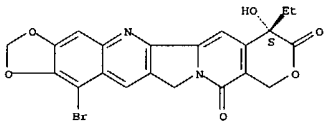
L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
NAME)

Absolute stereochemistry.



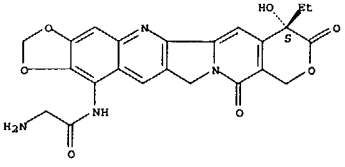
RN 135014-22-1 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-bromo-7-ethyl-7-hydroxy-, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 135014-23-2 CAPLUS
CN Acetamide, 2-amino-N-(7-hydroxy-7,8,11,13-tetrahydro-8,11-dioxo-10H-1,3-dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinolin-15-yl)-, monohydrochloride, (S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

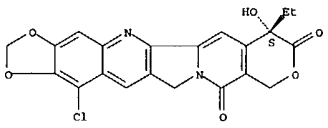


● HCl

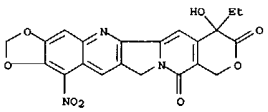
RN 135014-26-5 CAPLUS

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-chloro-7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

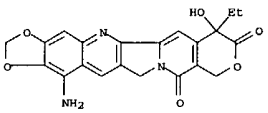
Absolute stereochemistry.



RN 135095-69-1 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-15-nitro- (9CI) (CA INDEX NAME)

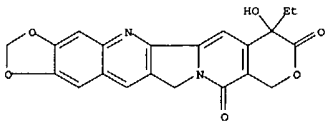


RN 135096-87-6 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 15-amino-7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



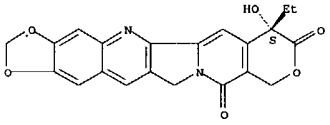
IT **104155-89-7DP**, analogs **135415-73-5DP**, analogs
RL: PREP (Preparation)
(preparation of, as antitumor agents)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

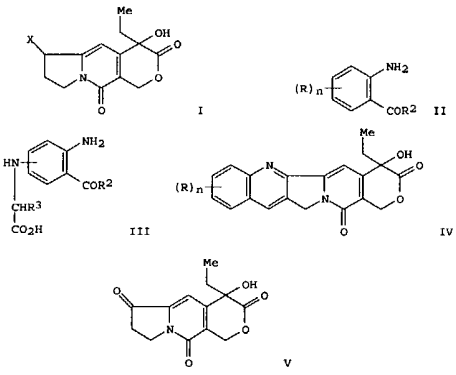


RN 135415-73-5 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy-, (7S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
GI

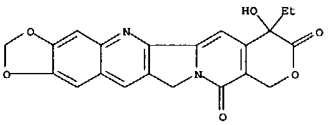


AB A method is claimed for synthesizing camptothecin and its analogs via lactone I (X = organic group which is converted to a carbonyl group when treated with an acid), which is deprotected and then reacted with aniline derivative II (R = cyano, methylenedioxy, formyl, OH, C1-8 alkoxy, NO2, amino, Cl, Br, etc.; R2 = H, C1-8 alkyl; n = 1-2) or III (R3 = side chain of any of the 20 naturally occurring amino acids). Also claimed are camptothecin analogs IV (R = amino acid amido group, C4-10 carboxylic acid amido group, urea group, etc.; n = undefined). A mixture of 4-methoxy-2-aminobenzaldehyde, ketone V, and p-MeC6H4SO3H in PhMe was refluxed for 2 h in a flask equipped with a Dean-Stark trap to give 11-methoxy-20(RS)-camptothecin (VI). A solution of VI in 48% aqueous HBr was refluxed for 6 h to give, after workup, 11-hydroxy-20(RS)-camptothecin which was active as antileukemic agent in mouse leukemia assays at 7.5-60 mg/kg.
AN 1990:611961 CAPLUS
DN 113:211961
TI Synthesis of camptothecin and its analogs as antitumor agents
IN Wall, Monroe E.; Wani, Mansukh C.; Nicholas, Allan W.; Manikumar, Govindarajan
PA Research Triangle Institute, USA
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
DT Patent
LA English
FAN.CNT 6

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9003169	A1	19900405	WO 1989-US4176	19890928
	W: AU, DK, JP, KR, NO				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	US 4981968	A	19910101	US 1988-250094	19880928
	AU 8944187	A1	19900418	AU 1989-44187	19890928
	EP 436653	A1	19910717	EP 1989-911645	19890928
	R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
PRAI	US 1988-250094	A	19880928		
	US 1987-32449	A2	19870331		
	WO 1989-US4176	A	19890928		

OS MARPAT 113:211961
IT **104155-89-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as antitumor agent)
RN 104155-89-7 CAPLUS
CN 10H-1,3-Dioxolo[4,5-g]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-8,11(7H,13H)-dione, 7-ethyl-7-hydroxy- (9CI) (CA INDEX NAME)



6/24/04

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'CAS' IS AN AMBIGUOUS FILE OR CLUSTER NAME
 CASLINK          - Linked CAS files (Predefined Search Sequences)
 CASRNS           - CAS Registry Numbers Cluster
 CA               - The Chemical Abstracts File 1907-present
 CASREACT         - The Chemical Abstracts Reaction Search Service
ENTER FILE OR CLUSTER NAME (IGNORE):end

=> file casreact
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      26.67     182.30

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -2.77      -2.77

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FILE CONTENT:1840 - 20 Jun 2004 VOL 140 ISS 25

************************************************************
*                                                          *
*     CASREACT now has more than  8 million reactions      *
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Some records from 1974 to 1991 are derived from the ZIC/VINITI data file
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data from the period prior to 1986.

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Crossover limits have been increased.  See HELP RNCROSSOVER for details.

Structure search limits have been raised.  See HELP SLIMIT for the new,
higher limits.

=> d his

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L2            21 S L1
L3           356 S L1 FUL

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L4           166 S L3
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L5            47 S L3/P
L6             0 S L5 AND AMINO CYANO
L7             4 S L5 AND CYANO

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100.0% DONE      2 VERIFIED       2 HIT RXNS                      1 DOCS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED VERIFICATIONS:          2 TO      124
PROJECTED ANSWERS:                1 TO       79

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100.0% DONE     41 VERIFIED      37 HIT RXNS                      7 DOCS
SEARCH TIME: 00.00.01

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FULL ESTIMATED COST                                     102.72     285.02

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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CA SUBSCRIBER PRICE                                       0.00      -2.77

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FILE COVERS 1907 - 24 Jun 2004  VOL 140 ISS 26
FILE LAST UPDATED: 23 Jun 2004  (20040623/ED)
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6/24/04

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> s l9
L10           7 L9

=> d abs bib fhitstr 1-7
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L10 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

AB Depletion of glutathione (GSH) in MCF-7 and MDA-MB-231 cell lines by pretreatment with the GSH synthesis inhibitor buthionine sulfoximine potentiated the activity of 10,11-methylenedioxy-20(S)-camptothecin, SN-38 [7-ethyl-10-hydroxy-20(S)-camptothecin], topotecan, and 7-chloromethyl-10,11-methylenedioxy-20(S)-camptothecin (CMMDC). The greatest potentiation was observed with the alkylating camptothecin CMMDC. Buthionine sulfoximine pretreatment also increased the number of camptothecin-induced DNA-protein crosslinks, indicating that GSH affects the mechanism of action of camptothecin. We also report that GSH interacts with CMMDC to form a stable conjugate, 7-(glutathionylmethyl)-10,11-methylenedioxy-20(S)-camptothecin (GSMMDC), which is formed spontaneously in buffered solns. and in MCF-7 cells treated with CMMDC. GSMMDC was synthesized and found to be nearly as active as 10,11-methylenedioxy-20(S)-camptothecin in a topoisomerase (topo) I-mediated DNA nicking assay. The resulting topo I cleavage complexes were remarkably stable. In cell culture, GSMMDC displayed potent growth-inhibitory activity against U937 and P388 leukemia cell lines. GSMMDC was not active against a topo I-deficient P388 cell line, indicating that topo I is its cellular target. Peptide-truncated analogs of GSMMDC were prepared and evaluated. All three deriva. [7-(γ-glutamylcysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, 7-(cysteinylglycylmethyl)-10,11-methylenedioxy-20(S)-camptothecin, and 7-(cysteinylmethyl)-10,11-methylenedioxy-20(S)-camptothecin] displayed topo I and cell growth-inhibitory activity. These results suggest that 7-peptidyl deriva. represent a new class of camptothecin analogs.

AN 2002:550586 CAPLUS

DN **138:162968**

TI Dual role of glutathione in modulating camptothecin activity: depletion potentiates activity, but conjugation enhances the stability of the topoisomerase I-DNA cleavage complex

AU Gamcsik, Michael P.; Kasibhatla, Mohit S.; Adams, David J.; Flowers, James L.; Colvin, O. Michael; Manikumar, Govindarajan; Wani, Mansukh; Wall, Monroe E.; Kohlhagen, Glenda; Pommier, Yves

CS Department of Medicine, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, NC, 27710, USA

SO Molecular Cancer Therapeutics (2001), 1(1), 11-20
CODEN: MCTOCF; ISSN: 1535-7163

PB American Association for Cancer Research

DT Journal

LA English

OS CASREACT 138:162968

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A process was developed for the preparation of the camptothecin derivative 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (I) by cyclizing the (dioxinoquinolinylmethyl)pyranopyridinedionesa II (X = Cl, Br, or iodo) and optionally resolving the mixture to obtain the desired enantiomer, and/or if desired, converting the resulting compound of formula I or a salt thereof into a physiol. acceptable salt or solvate thereof. Thus, 4(S)-4-ethyl-4-hydroxy-7-[7-iodo-9-(4-methylpiperazin-1-ylmethyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinolin-8-ylmethyl]-4,7-dihydro-1H-pyrano[3,4-c]pyridine-3,8-dione was cyclized by treatment with palladium acetate, potassium carbonate, and triphenylphosphine in anhydrous acetonitrile to give 7-(4-methylpiperazinomethyl)-10,11-ethylenedioxy-20(S)-camptothecin.

AN 2000:321541 CAPLUS

DN **132:334656**

TI Preparation of a camptothecin derivative by intramolecular cyclization

IN Fang, Francis Gerard; Huie, Edward Mcdonald; Xie, Shiping; Comins, Daniel L.

PA Glaxo Wellcome Inc., USA; North Carolina State University

SO U.S., 14 pp., Cont.-in-part of U.S. 5,491,237.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6063923	A	20000516	US 1996-737032	19961101
	US 5491237	A	19960213	US 1994-237081	19940503
	WO 9529919	A1	19951109	WO 1995-US5427	19950502
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	EP 1254908	A1	20021106	EP 2002-14439	19950502
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
	US 6462196	B1	20021008	US 2000-552214	20000419
	US 2003045719	A1	20030306	US 2002-243470	20020913
	US 6559309	B2	20030506		
	US 2003204088	A1	20031030	US 2003-395806	20030324
PRAI	US 1994-237081	A2	19940503		
	WO 1995-US5427	W	19950502		

L10 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

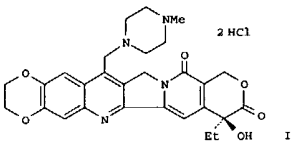
	EP 1995-918904	A3	19950502
	US 1996-737032	A1	19961101
	US 2000-552214	A3	20000419
	US 2002-243470	A1	20020913

OS CASREACT 132:334656; MARPAT 132:334656

RE.CNT 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB The topoisomerase I inhibitor GI147211C (I) has shown to have promising anti-cancer properties. To fully assess the clin. potential of I an improved synthesis of the drug substance was required. A convergent catalytic asym. synthesis of I via key steps including two Heck reactions, a Sharpless asym. dihydroxylation, and a Mitsunobu reaction is described. A 2-chloroquinoline is shown to be a viable substrate for the final Heck reaction to generate the camptothecin nucleus.

AN 1997:553117 CAPLUS

DN **127:262890**

TI Convergent catalytic asymmetric synthesis of camptothecin analog GI147211C

AU Fang, Francis G.; Bankston, Donald D.; Huie, Edward M.; Johnson, M. Ross; Kang, Kyung-Chol; LeHoullier, Craig S.; Lewis, George C.; Lovelace, Thomas C.; Lowery, Melissa W.; McDougald, Darryl L.; Meerholz, Clive A.; Partridge, John J.; Sharp, Matthew J.; Xie, Shiping

CS Chemical Development Department, Glaxo Wellcome Inc., Research Triangle Park, NC, 27709, USA

SO Tetrahedron (1997), 53(32), 10953-10970
CODEN: TETRAB; ISSN: 0040-4020

PB Elsevier

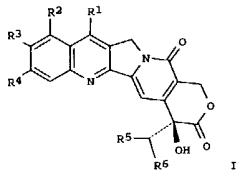
DT Journal

LA English

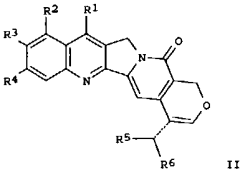
OS CASREACT 127:262890

RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I



II

AB The camptothecins I (R1, R2 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl, aminomethyl; R3, R4 = H, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, hydroxyalkyl, alkoxyalkyl; R3R4 = OCCH2O, OCH2CH2O; R3 = carbamoyloxy; R5, R6 = H, alkyl) were prepared from the pyranoindolizinoquinolinones II. Thus, the pyranoindolizinoquinolinone I (R1 = 4-methylpiperazinomethyl, R2 = R5 = H, R3R4 = OCH2CH2O, R6 = Me) was treated with AD-mix-β containing hydroquinidine 1,2-phthalazinediyl diether in H2O-Me4COH, followed by Swern oxidation to give the camptothecine derivative II.
AN 1997:385708 CAPLUS
DN **127:5227**
TI Method for preparing camptothecin derivatives
IN Fang, Francis G.; Xie, Shiping
PA Glaxo Wellcome Inc., USA; Fang, Francis G.; Xie, Shiping
SO PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

L10 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9716454	A1	19970509	WO 1996-US17574	19961101
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG				
	CA 2236420	AA	19970509	CA 1996-2236420	19961101
	AU 9676038	A1	19970522	AU 1996-76038	19961101
	AU 717315	B2	20000323		
	EP 876373	A1	19981111	EP 1996-938728	19961101
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11515028	T2	19991221	JP 1997-517588	19961101
	JP 3499246	B2	20040223		
	NZ 322318	A	20000128	NZ 1996-322318	19961101
	PL 186540	B1	20040130	PL 1996-326869	19961101
	NO 9801970	A	19980630	NO 1998-1970	19980430
	US 6143891	A	20001107	US 1998-68185	19980514
	US 6284891	B1	20010904	US 2000-638945	20000815
	US 2001051724	A1	20011213	US 2001-903101	20010711
	US 6716982	B2	20040406		
PRAI	US 1995-6138P	P	19951102		
	WO 1996-US17574	W	19961101		
	US 1998-68185	A3	19980514		
	US 2000-638945	A3	20000815		
OS	CASREACT 127:5227; MARPAT 127:5227				

L10 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The present invention relates to a method for the preparation of camptothecin and camptothecin-like compds. and to novel intermediates used in this preparation In particular, the invention provides a process for the preparation of the camptothecin derivative, 7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20-(R,S)-camptothecin (I), which comprises cyclizing the compound of formula (II, X = halogen, particularly chloro, bromo, or iodo); and when the compound of formula I is obtained as a mixture of enantiomers optionally resolving the mixture to obtain the desired enantiomer; and/or if desired, converting the resulting compound of formula I or a salt thereof into a physiol. acceptable salt or solvate thereof.
AN 1996:106450 CAPLUS
DN **124:146561**
TI Preparation of a camptothecin derivative by intramolecular cyclization
IN Fang, Francis Gerard; Huie, Edward Mcdonald; Xie, Shiping; Comins, Daniel L.
PA Glaxo Wellcome Inc., USA; North Carolina State University
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9529919	A1	19951109	WO 1995-US5427	19950502
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5491237	A	19960213	US 1994-237081	19940503
	AU 9524651	A1	19951129	AU 1995-24651	19950502
	EP 758335	A1	19970219	EP 1995-918904	19950502
	EP 758335	B1	20021106		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	JP 09512559	T2	19971216	JP 1995-528482	19950502
	EP 1254908	A1	20021106	EP 2002-14439	19950502
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV				
	AT 227292	E	20021115	AT 1995-918904	19950502
	ES 2188661	T3	20030701	ES 1995-918904	19950502
	US 6063923	A	20000516	US 1996-737032	19961101
	US 6462196	B1	20021008	US 2000-552214	20000419
	US 2003045719	A1	20030306	US 2002-243470	20020913
	US 6559309	B2	20030506	US 2003-395806	20030324

L10 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

PRAI	US 1994-237081	A2	19940503		
	EP 1995-918904	A3	19950502		
	WO 1995-US5427	W	19950502		
	US 1996-737032	A1	19961101		
	US 2000-552214	A3	20000419		
	US 2002-243470	A1	20020913		
OS	CASREACT 124:146561; MARPAT 124:146561				

L10 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

AB The synthesis and antitumor activities of the novel water soluble camptothecin deriva. 7-[(4-methylpiperazino)methyl]-10,11-(methylenedioxy)-(20S)-camptothecin trifluoroacetate (I) and 7-[(4-methylpiperazino)methyl]-10,11-(ethylenedioxy)-(20S)-camptothecin trifluoroacetate (II) are described. The solubilities of I and II were measured to be 4.5 and 5.8 mg/mL, resp., in pH 5 acetate buffer in contrast to <0.003 mg/mL for camptothecin in the same buffer. In the purified topoisomerase I cleavable complex enzyme assay, I and II demonstrated potent inhibition of topoisomerase I with IC50's of 300 and 416 nM, resp., in comparison to 679 nM for camptothecin and 1028 nM for topotecan. In human tumor cell cytotoxicity assays, I and II demonstrated potent antitumor activity against ovarian (SKOV3), ovarian with upregulated MDR-P1 glycoprotein (SKVLB), melanoma (LOX), breast (T47D), and colon (HT29) with IC50's ranging from 0.5 to 102 nM. I and II induced tumor regressions in the HT29 human colon tumor xenograft model and demonstrated similar rank order of potency compared to in vitro assay results.

AN 1995:320183 CAPLUS

DN **122:81718**

TI Synthesis and Antitumor Activity of Novel Water Soluble Derivatives of Camptothecin as Specific Inhibitors of Topoisomerase I

AU Luzzio, Michael J.; Besterman, Jeffrey M.; Emerson, David L.; Evans, Michael G.; Lackey, Karen; Leitner, Peter L.; McIntyre, Gordon; Morton, Bradley; Myers, Peter L.; et al.

CS Department of Medicinal Chemistry, Glaxo Research Institute, Research Triangle Park, NC, 27709, USA

SO Journal of Medicinal Chemistry (1995), 38(3), 395-401
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

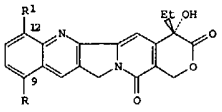
DT Journal

LA English

OS CASREACT 122:81718

L10 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB Eight optically active and nine racemic ring A modified analogs of 20(S)-camptothecin, e.g. I (R = NO2, NH2, R1 = H; R = H, R1 = NO2, H), were prepared and evaluated for antitumor activity in the L-1210 leukemia system. Thus, 20(S)-camptothecin was nitrated with fuming HNO3-H2SO4 to give I (R = NO2, R1 = H; R = H, R1 = NO2), which were reduced to give I (R = NH2, R1 = H; R = H, R1 = NH2). The ring A mono- and disubstituted analogs displayed a wide variance in activity and potency. Monosubstitution by NH2 or OH at positions 9, 10, or 11 yielded compds. with activity much higher than the parent compound, camptothecin, whereas substitution at position 12 greatly reduced activity. In general, disubstitution in ring A greatly reduced antileukemic activity. Replacement of ring A by heterocyclic rings (thiophene or pyridine) leads to analogs with only moderate activity.

AN 1987:33362 CAPLUS

DN **106:33362**

TI Plant antitumor agents. 23. Synthesis and antileukemic activity of camptothecin analogs

AU Wani, Mansukh C.; Nicholas, Allan W.; Wall, Monroe E.

CS Research Triangle Inst., Research Triangle Park, NC, 27709, USA

SO Journal of Medicinal Chemistry (1986), 29(11), 2358-63
CODEN: JMCMAR; ISSN: 0022-2623

DT Journal

LA English

OS CASREACT 106:33362

6/24/04

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